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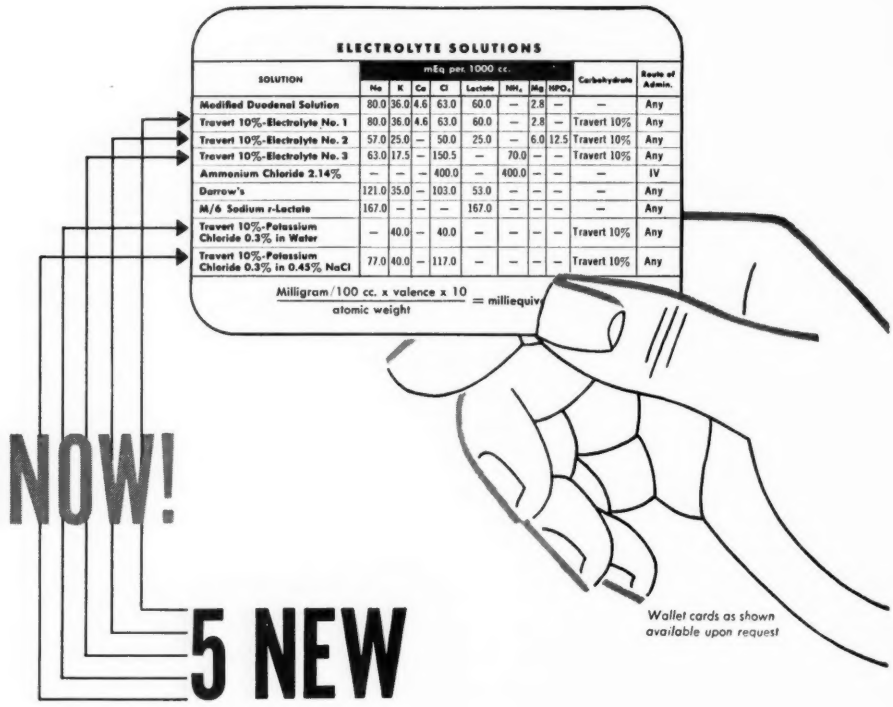
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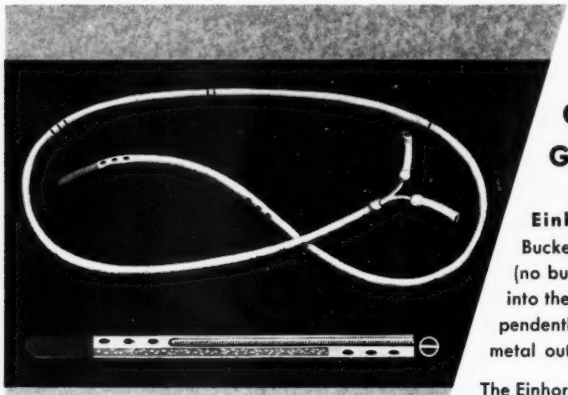

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EMERGENCY SURGICAL TREATMENT OF PERFORATED GASTRIC AND DUODENAL ULCERS

OLIVER H. BEAHRS, M.D., F.A.C.S., DOUGLAS K. DUNCAN, M.D., and LEWIS A. VADHEIM, M.D., Rochester, Minnesota

IN recent years, nonsurgical treatment of perforated peptic ulcer has attracted much attention, culminating in 1951 with a report by Seeley on the results of ch treatment in 110 cases. The footnote to ble I explains that, from another point of w, Seeley's series consisted of 106 cases.

During the past two decades, several fac- rs have served to lower the mortality rate m perforated peptic ulcer treated either by surgical or the nonsurgical method (Table These factors have included improve- nts in anesthesia, increasing use of whole od and of plasma volume expanders, in- asing knowledge of fluid and electrolyte lance, introduction of continuous gastric tion, and use of chemotherapeutic and tibiotic agents.

As it may be misleading to compare the re- ts of nonsurgical treatment of perforated ptic ulcer at the present time with the re- ts of surgical treatment of perforated pep- ulcer in the past, we believe that the cur- nt results obtained in cases of surgically treated gastric and duodenal perforation should be reported.

MATERIAL

The present study, therefore, includes all cases in which surgical treatment was applied for acute, free perforation of ulcer of the stomach or duodenum at the Mayo Clinic during the decade preceding January 1, 1951. One hundred fourteen cases are included in the series.

Sex and age of patients. Of the 114 patients with perforated peptic ulcer who are subjects of this report, 107 were males and 7 were females. These figures include 3 males, each of whom had a second perforation. The age distribution of the patients was as follows: less than 20 years, 3; 20 to 29 years, 9; 30 to 39 years, 18; 40 to 49 years, 29; 50 to 59 years, 30; 60 to 69 years, 18; 70 to 79 years, 6, and more than 79 years, 1.

Our patients were materially older than those reported by Seeley. The peak incidence of gastroduodenal perforation in our group was in the decade of life 50 to 59 years, while in Seeley's 106 cases the peak incidence was in the decade 20 to 29 years. While 73.7 per cent of our patients were 40 years of age or older, only 30.1 per cent of Seeley's patients were 40 years old or older.

The relation of age to mortality in cases of perforated peptic ulcer is well known. In DeBakey's statistical analysis, the mortality rate among patients in the decade of life 30 to 39 years was 18.9 per cent and the figure rose to 50 per cent among patients who were more than 50 years of age. Seeley's 4 patients who were moribund on admission were aged 39, 40, 43, and 53 years; he did not give the age of his other patient who died. Our own

From the Division of Surgery, Mayo Clinic, and the Department of Surgery, Mayo Foundation, Rochester, Minnesota.

TABLE I.—MORTALITY IN CASES OF PERFORATED PEPTIC ULCER

Author	No. of cases	Years	Treatment	Mortality, per cent
Richardson	103	1894–1915	Surgical	44.2
Ulfelder and Allen	334	1916–1940	Surgical	26.9
DeBakey (collected series)	15,340	1940	Surgical	23.4
Black and Blackford	93	1935–1945	Surgical	12
Estes and Bennett	83	1944	Surgical	8.7
Graham	130	1946	Surgical	6.8
Baritell	88	1947	Surgical	1.1
Vaughn and Warren	70	1950	Surgical	1.4
Seeley	110*	1945–1951	Nonsurgical	4.5*
Heslop et al.	104	1947–1952	Surgical	8.6
Heslop et al.	104	1947–1952	Nonsurgical	8.6
Present series	114	1941–1951	Surgical	2.6

*Over-all mortality; includes 4 patients moribund when admitted. Of 106 remaining patients 1 died (0.9 per cent).

deaths were of patients aged 32, 62, and 75 years.

Site of perforation. In our series the site of perforation was the stomach in 7 cases; the pylorus in 10 cases, and the duodenum in 97 cases. This is important since the possibility of malignancy must be considered in all cases of gastric ulcer. The only certain way to rule out malignancy of a gastric ulcer is by examination of the entire ulcer. In 3 of the 7 cases of perforated gastric ulcer, primary gastric resection was performed shortly after perforation; recovery was uneventful.

Duration of symptoms of ulcer. Symptoms of ulcer were recorded as absent in 12 cases. The duration of symptoms was less than 1 year in 18 cases, between 1 and 4 years in 20 cases, between 5 and 9 years in 23 cases, between 11 and 19 years in 27 cases, and more than 19 years in 13 cases. In 1 case no mention was made of previous symptoms of ulcer.

Interval between time of perforation and operation. The interval between perforation and operation was less than 6 hours in 61 cases, 6 to 11 hours in 36 cases, 12 to 17 hours in 10 cases, 18 to 23 hours, 30 hours, 38 hours, and 40 hours in 1 case each, and 48 hours in 2 cases. The interval was not stated in 1 case.

In our group, therefore, the interval between perforation and the institution of treatment was similar to that in Seeley's group. Of our patients, 85.1 per cent were subjected to exploration less than 12 hours after the perforation, while treatment of 84.9 per cent of Seeley's group of 106 patients was begun less than 12 hours after perforation.

TREATMENT

The procedures carried out in the 114 cases of perforated peptic ulcer were as follows: simple closure of defect, 99 cases; simple closure of defect and appendectomy, 3 cases; simple closure of defect and removal of carcinoma of ovary, 1 case; simple closure of defect and gastroenterostomy, 5 cases, and subtotal gastric resection, 6 cases.

It is our belief that simple closure of the perforation should be followed by the best rate of immediate recovery. Other procedures were done infrequently and only for special indications. Gastroenterostomy was performed when it appeared that the duodenal lumen had been compromised by closure of the defect in its wall. Three of the 6 gastric resections were done for perforated gastric ulcer.

One or more antibiotic or chemotherapeutic agents were given at some time during the illness of 104 (91.2 per cent) of the patients. Continuous gastric suction was used postoperatively in 96 (84.2 per cent) of our cases and usually was continued for from 3 to 5 days. At the end of this time the tube was removed and oral feedings were begun.

FATALITIES

Of our 114 patients, 3 died.

CASE 1. A man, 75 years old, whose pyloric perforation was 1 centimeter in diameter, underwent surgical operation 8 hours after onset of symptoms. After simple closure of the perforation, recovery was uncomplicated and he was dismissed from the hospital on the eleventh postoperative day. Four days later he was readmitted with "weakness and depression." After apparently recovering from this episode he died suddenly on the thirty-second postoperative day. Necropsy disclosed occlusion of the superior mesenteric artery and multiple recurrent pulmonary emboli, with focal infarction of the right lower and left upper lobes.

CASE 2. A man, 62 years old, had symptoms of perforation 30 hours before his admission to hospital. He was markedly dehydrated, pulseless, and anuric. Following surgical closure of the perforation in the anterior surface of the duodenum, the patient did not

respond. He died 2 days later. Necropsy was not performed.

CASE 3. A woman, 32 years of age, had had duodenal ulcer for 3 years. Finally perforation occurred and, 5 hours thereafter, surgical operation was performed. Following closure of the defect in the superior duodenal wall, and in spite of administration of antibiotics, use of continuous gastric suction, and other supportive measures, the patient died from peritonitis on the fourth postoperative day. In this case, however, as in Case 2, a necropsy was not performed.

COMPLICATIONS

The incidence of complications is influenced when surgical treatment is applied in cases of perforated peptic ulcer. Complications referable to the abdominal incision are absent, obviously, if such an incision is not made. Of 114 cases, 1 complication relative to the wound occurred in each of 16 cases (14.0 per cent) as follows: infection of the wound, 13 cases; separation of edges of wound requiring secondary closure, hematoma of wound, and duodenal fistula requiring gastric resection, 1 case each. Because of these complications, further surgical measures were required in 2 cases. In the other 14 cases, the complications did not substantially retard convalescence.

The remaining complications were results of the gastrointestinal perforation or were such as might be expected in any serious illness. Cases in which complications of this kind occurred, numbered 18; in these 18 cases a total of 28 complications were encountered. They were as follows: gastric retention, 6 cases; thrombophlebitis, 5 cases; toxic psychosis, 4 cases; pulmonary emboli (nonfatal), pneumonitis, and upper gastrointestinal bleeding, 3 cases each; empyema, abscess of right lower quadrant, auricular fibrillation, and parotitis, 1 case each.

In Seeley's 106 cases, 16 complications were listed, apparently 1 complication to 1 case: subphrenic abscess, 4; right pleural effusion, 4; drug psychosis, 2; pneumonitis, 1; thrombophlebitis, 1; upper abdominal abscess, 2; pelvic abscess, 2. Comparison of Seeley's experience with ours demonstrates that there were fewer abscesses in the surgically treated group than in Seeley's nonsurgically treated group.

STAY IN HOSPITAL

It has been declared by Heslop and associates that recovery is more rapid in cases in which conservative treatment is employed than in those in which treatment is surgical. Possibly that declaration is based on Heslop's impressions from his own experience, for we did not find in the literature which we read a record of an experience on which the declaration might be based. Although Seeley did not give figures on the length of hospitalization, he wrote that "by the fourteenth day, in the absence of complication," the patients were transferred to the medical service. The average stay in hospital of the 111 surviving patients in our series was 16.9 days, in spite of the fact that 3 patients remained in hospital 58, 77, and 92 days respectively. The patient who remained longest in hospital was detained because of an orthopedic problem.

COMMENT

When any nonsurgical method of treatment is used for the condition considered here, the question will be asked: "How do you know that you are dealing with a perforated peptic ulcer?" You do not know, for certain, short of surgical exploration. Observation of the course of the illness, and subsequent roentgenologic examination, go far to reduce the error in nonsurgical cases but do not eliminate it. A second question is: "How can you be sure that you are not dealing with a large gastric or duodenal perforation and such gross flooding as to threaten the natural tendency of a hole to seal off?" You cannot be sure; there is no way short of early exploration to answer the question. Here is the most serious responsibility facing the physician who uses nonsurgical treatment; namely, to assign for operation the cases which are unfavorable for nonsurgical treatment. For these reasons we cannot abandon our belief that surgical operation is the treatment of choice for perforated peptic ulcer.

On the other hand, the physician who uses only the surgical approach to treatment of perforated peptic ulcer occasionally will perform exploration of a victim of coronary thrombosis, acute pancreatitis, or pneumonia —with unfortunate results. However, with

knowledge of the excellent results obtained by Seeley, treatment may justifiably be conservative in cases in which there is a reasonable doubt about the diagnosis. In addition, it may be wise to treat conservatively those patients who present themselves for treatment so long after the perforation has taken place that either they are moribund or their peritoneal infection appears to have become localized.

SUMMARY

Review was made of all cases in which perforated peptic ulcer was treated surgically at the Mayo Clinic in the decade preceding January 1, 1951. Of 114 patients, 3 died, giving a mortality rate of 2.6 per cent.

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THE DETECTION OF CHROMOSOMAL SEX IN HERMAPHRODITES FROM A SKIN BIOPSY

KEITH L. MOORE, M.Sc., MARGARET A. GRAHAM, M.Sc., and MURRAY L. BARR, M.D., London, Ontario, Canada

A CASE of hermaphroditism presents to the physician an exceedingly difficult problem. The tragic status of the patient demands that measures be taken to correct the developmental error, in so far as this is possible. There is little agreement, however, concerning the etiology of hermaphroditism, the criteria on which a decision as to the dominant sex are to be based, or the management of individual cases. In brief, the problem of hermaphroditism appears to have reached an impasse and a new approach is desirable.

Painter, and Evans and Swezy have shown that in humans, females have an XX chromosome combination while males have XY chromosomes as the sex chromosomes. The Y chromosome is small relative to the size of the X chromosome. We have found that the nature of the sex chromosomes (XX or XY) in an individual may be detected by examining the epidermal nuclei in a small biopsy of skin. This technique offers a new approach to the vexatious problem of hermaphroditism.

NORMAL SEX DIFFERENTIATION

Sex is determined at fertilization depending on whether the ovum, with its single X chromosome, is fertilized by a sperm bearing an X or a Y chromosome. Sex differentiation does not begin until the seventh or eighth week of intrauterine life when the previously indifferent gonads show signs of developing into ovaries or testes. Both sex chromosomes and certain autosomes (chromosomes other than the sex chromosomes) bear genes which are concerned with gonadal differentiation. The balance between genes, with a sex-determining function, on the XX chromosomes and similar genes on the autosomes causes the indifferent gonads to develop into ovaries, while the balance between sex-determining genes on the XY chromosomes and autosomes directs indifferent gonads toward development of testes.

A wolffian or male genital duct system and a müllerian or female genital duct system both appear during early embryonic development. The external genitalia develop from sexually indifferent structures. There is disagreement concerning the factors which direct the development of wolffian or müllerian derivatives and the appropriate maturation of the anlage of the external genitalia in later stages. Since the classical work of Lillie on the freemartin in cattle, the majority of biologists have adopted the view that sex hormones of the fetal gonads are responsible for the differentiation of the genital system, once definitive ovaries or testes have been formed. This view is summarized well by Greene (7). Moore (12), on the other hand, was unable to reproduce the freemartin condition by experimental treatment of embryos with sex hormones. He expresses the minority opinion that the gonads do not produce sex hormones during fetal life and that sex differentiation during the intrauterine period is a genetically controlled process without the intervention of sex hormones. Resolution of this problem will be helpful in the eventual understanding of the etiology of developmental sex abnormalities.

TYPES OF HERMAPHRODITISM AND ABNORMAL SEX DIFFERENTIATION

In reviewing the literature on hermaphroditism one is impressed by the kaleidoscopic nature of the condition, produced by many variables appearing in diverse combinations. The Klebs classification, whatever its shortcomings may be, is in common use and has served to systematize this complex developmental abnormality.

From the Department of Anatomy, Faculty of Medicine, University of Western Ontario, London, Canada.

This work was made possible by grants-in-aid to one of the authors (M.L.B.) from the National Cancer Institute and the National Research Council of Canada.

According to the Klebs classification there are true hermaphrodites and pseudo hermaphrodites. The criterion of true hermaphroditism is the presence of ovarian and testicular tissue, either as an ovotestis or as a separate ovary and testis. There is great variability in the anatomy of the external and internal genitalia, in body form and in psychosexual outlook. Such cases are rare, about 50 histologically proved cases of true hermaphroditism having been recorded in the literature.

Pseudohermaphrodites are classified as "male" or "female" depending on whether the gonads are testes or ovaries. The male pseudohermaphrodite group is further subdivided into internal and external types, the former having müllerian duct derivatives in addition to whatever abnormality may be present in the external genitalia. As in the true hermaphrodite group, pseudohermaphrodites show great variation in the morphology of the genital organs, in body form, breast development, growth of hair, as well as in their psychosexual manifestations. Pseudohermaphroditism appears to be more common than is usually thought, the incidence being, according to Young, 1 in 1,000 of the population.

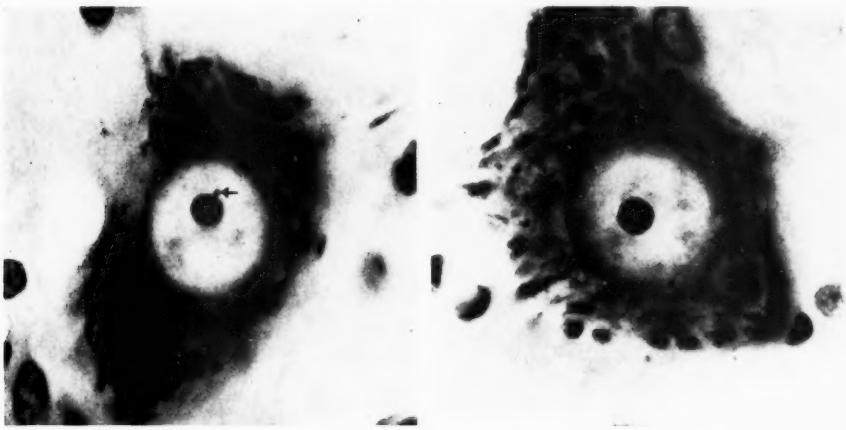
The primary importance which is attached to the gonads is a disquieting feature of this classification. The secondary sex characteristics in pseudohermaphrodites often run counter to the type of gonad. Absurdities result if the Klebs nomenclature is carried over literally into the management of certain cases. It is possible that a new and more reliable classification, based on the sex chromosomes, will arise out of the present work.

The etiology of hermaphroditism in general is not sufficiently well known to merit comment at this time. Two points, however, do stand out clearly. First, regardless of whether or not homones participate in normal fetal sex differentiation, it is certain that some types of hermaphroditism are caused by hormonal dysfunction during fetal life. This applies especially to the large proportion of female pseudohermaphrodites showing the adrenogenital syndrome. In these cases, hyperplasia of the fetal adrenal cortex with excessive production of androgens (often at the expense of other cortical hormones) directs the maturation of the genitalia in a female fetus in the male direction. An androgen-producing tumor in the mother may also cause female pseudohermaphroditism in the child, although such cases are necessarily rare. An especially interesting example was described by Bretnall, the tumor in this instance being an arrhenoblastoma of the ovary. The second well established fact in etiology is the genetic basis of many cases of hermaphroditism of all types, as shown by their familial incidence. A thorough study of the genetics of hermaphroditism would be well worth while. With the exception of the role of the adrenal cortex in one group of cases and the genetic background of many cases of hermaphroditism the etiology of the abnormality is obscure in most important aspects.

PRELIMINARY INVESTIGATIONS WHICH LEAD TO THE DETECTION OF CHROMOSOMAL SEX IN MAN FROM SKIN BIOPSIES

The following brief summary will show that the detection of chromosomal sex in man rests on a firm basis of animal observations.

Tissues of the cat have been studied most extensively. Nerve cell nuclei are most suitable for this work because they are large and vesicular. Nuclear details are obscured in small, pycnotic nuclei. In nerve cell nuclei of the female cat there is, in addition to the large nucleolus, a chromatin mass about 1 micron in diameter. A chromatin body of similar size is seldom seen in nerve cell nuclei of male cats. The chromatin mass is called the sex chromatin in view of its size relation to sex. This sex difference in nuclear morphology is seen to best advantage in larger neurons which are less likely to contain multiple chromatin particles in their nuclei, which make the identification of sex chromatin more difficult. Typical female and male neurons of the cat are illustrated in Figure 1 a and b. The sex chromatin is most frequently adjacent to the nucleolus, as shown in Figure 1 a, but it may be free in the nucleoplasm or adjacent to the nuclear membrane. The sex chromatin gives positive cytochemical tests for desoxyribose nucleic acid. Further details concerning nuclear morphology in nerve cells of the cat have been recorded by Barr, Bertram, and Lindsay.



a b

Fig. 1. a, Motor neuron in the ventral horn of the spinal cord of a *female* cat. The sex chromatin, indicated by the arrow, is adjacent to the nucleolus. Cresyl violet. ×1,000. b, Motor neuron in the ventral horn of the spinal cord of a *male* cat. There is no visible sex chromatin. Occasional male nerve cells show a small mass of chromatin which may be sex chromatin but it is not as large as the typical sex chromatin of female nerve cells. Cresyl violet, ×1,000.

raham and Barr showed that a similar sex fference in nuclear morphology is present in sues and organs of the cat generally. In lls other than neurons, however, the sex romatin takes the form of a planoconvex dy with its flattened surface against the uclear membrane. Moore and Barr (13) ade a comparative study of nerve cell nuclei several mammals. A sex difference in the uclei, similar to that noted for the cat, was und in the following species—dog, mink, arten, ferret, raccoon, skunk, goat, and eer. The rodents which were studied (guinea g, rat, mouse, hamster, and ground hog) and he rabbit (a lagomorph) are nonconformists this regard. Their nerve cell nuclei contain ultiple chromatin bodies, adjacent to the ucleolus as a rule, and a sex difference could ot be detected. Prince demonstrated a sex difference in nuclear morphology throughout the nervous system of Macacus rhesus. A preliminary general survey of human tissues indicates that the distinctive nuclear morphology, according to sex, is present in man as in many lower animals. With this background, a systematic study of nuclei in human skin was made, because of the availability of this tissue as a biopsy in clinical medicine.

There are good reasons for inferring that the sex chromatin is derived from the sex chromosomes, although direct proof is lacking. The desoxyribose nucleic acid content of the sex chromatin relates it to the chromosomes, which also contain the desoxyribose type of nucleic acid. The sex chromosomes tend to remain compact and deeply staining (i.e. they are heteropycnotic or heterochromatic) when the other chromosomes or autosomes are so diffuse that it is difficult or impossible to identify them individually. This heterochromatic behavior of the sex chromosomes has long been known in developing male germ cells, as shown by Painter for man. Further, Geitler has clearly demonstrated a sex difference in nuclear morphology in somatic cells of insects, on the basis of the heterochromatic property of their sex chromosomes. It is likely, therefore, that in many mammals, including man, the heterochromatic portions of the two X chromosomes of female cells fuse to form a mass of chromatin which is sufficiently large to be readily visible. The small size of the Y chromosome is probably contributory to the minute size of the sex chromatin in male nuclei, rendering it an inconspicuous nuclear constituent with standard microscopic equip-

ment. In general, therefore, it is possible to establish whether nuclei contain XX or XY sex chromosomes on the basis of the size of the sex chromatin and the ease with which it can be identified in a representative sample of nuclei.

THE SEX CHROMATIN OR CHROMOSOMAL SEX IN HUMAN SKIN

Materials and methods. Since others may wish to apply this method of determining chromosomal sex the methods used will be described in some detail.

Specimens of skin from 50 female and 50 male subjects were studied. There were 20 biopsy specimens (10 female and 10 male). The remaining specimens were obtained mainly at autopsy; a few came from the operating room. The genital systems of all subjects were normal to the best of our knowledge. The ages of the subjects ranged from the newborn to 90 years.

The biopsies were taken from staff and students by Dr. W. E. Pace. Although the region from which the biopsy is taken seems unimportant for this work, the extensor surface of the forearm was used as a matter of routine. The area was anesthetized by subcutaneous infiltration of procaine. A small piece of skin, about 0.3 by 0.6 centimeter, was removed and the wound closed with 2 dermal sutures.

Of the various fixatives tried, the following proved most satisfactory. The specimens were fixed for 24 hours in a modified Davidson's solution which has the following formula: formalin 20 parts, 95 per cent alcohol 30 parts, glacial acetic acid 10 parts, and distilled water 30 parts (the 10 parts of glycerine in the original Davidson's solution are omitted). The specimens were then immersed for 24 to 48 hours in 70 per cent alcohol with several changes of solution. A biopsy should be in 70 per cent alcohol for mailing to a distant laboratory, if this is necessary. Routine embedding in paraffin was followed by sectioning at 5 microns.

Sections stained with hematoxylin and eosin are quite satisfactory for the identification of sex chromatin. Best results were obtained by preparation of the hematoxylin according to the method of Harris as described by Gatenby and Beams (4, section 288). The Feulgen technique, as outlined by Stowell, is also useful since the sex chromatin gives a positive Feulgen reaction because of its desoxyribose nucleic acid content. The nucleolus, containing ribose nucleic acid, is Feulgen-negative.

The sections were studied with an oil immersion objective, attention being directed toward the nuclei of the malpighian layer of the epidermis. A work sheet containing 100 circles representing nuclear outlines is useful. The sex chromatin is drawn in the circle when it can be identified. A minimum of 100 nuclei, selected at random, should be examined in this way and the incidence of visible sex chromatin recorded as a percentage figure.

OBSERVATIONS

Female specimens (Fig. 2 a, b, and c). In most nuclei the sex chromatin is a single, planoconvex body lying against the nuclear membrane. Occasionally the sex chromatin is free in the nucleoplasm or adjacent to the nucleolus. The sex chromatin stains deeply with hematoxylin but there may be a minute pale area within the chromatin mass. In the 50 specimens examined the sex chromatin was visible in from 52 to 85 per cent of nuclei, with an average incidence of 69 per cent. In general it may be said that the sex chromatin can be identified in about two-thirds of the nuclei in 5 micron sections of female epidermis. The real incidence is undoubtedly higher since the sex chromatin will be excluded from the section in some nuclei.

The sex chromatin is recognized most easily when it lies at the periphery of the optical section through the nucleus. With some experience the sex chromatin can also be identified when it lies against a part of the nuclear membrane which is oblique or perpendicular to the optical axis of the microscope. The sex chromatin is Feulgen-positive and stains with methyl green showing that its nucleic acid content is mainly of the desoxyribose type. In addition to one or more nucleoli, which stain less darkly than the sex chromatin, the nucleus contains particulate chromatin with the same staining properties as the sex chromatin. The sex chromatin can be distinguished from unrelated chromatin particles because of its

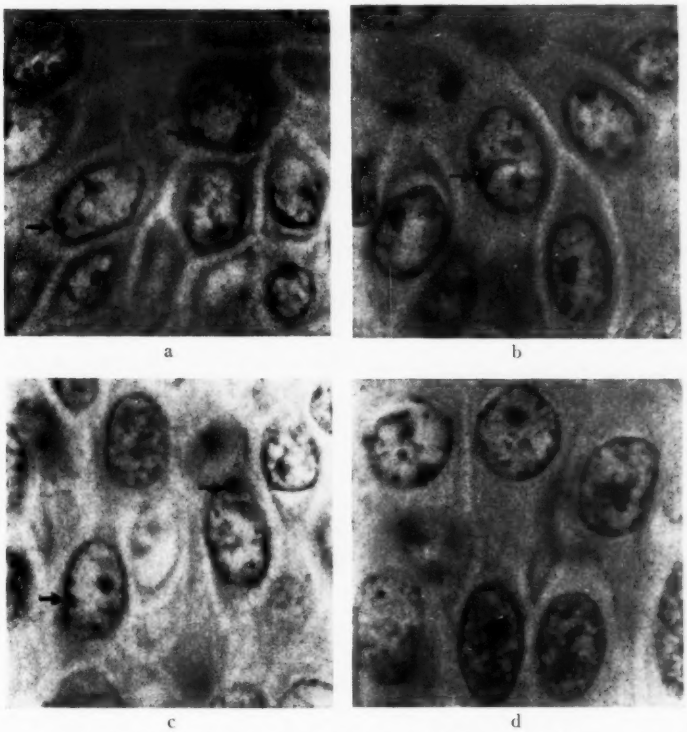


Fig. 2. a, b, and c, Photomicrographs of the malpighian layer of human *female* epidermis. The sex chromatin is indicated by the arrows. By focusing through the thickness of the section, two-thirds of the nuclei are found to contain a mass of sex chromatin located at the periphery of the optical section through the nucleus, as illustrated, or oriented in a different manner. Hematoxylin and eosin, ×1,600. d, Photomicrograph of the malpighian layer of human *male* epidermis. Sex chromatin is not visible in the nuclei and this illustration is characteristic of all focal planes through the section. Hematoxylin and eosin, ×1,600.

larger size, its planoconvex outline when lying against the nuclear membrane as seen in optical section and, at times, the small pale area within the chromatin mass. As noted before, the data available at this time indicate that the sex chromatin of female cells is formed by fusion of heterochromatic regions of the two X chromosomes.

Typical female nuclei are illustrated in Figure 2 a, b, and c, the sex chromatin being indicated by arrows. It is unusual to encounter more than one or two sex chromatin masses in exactly the same focal plane of a field under the high magnification necessary for this work. By focusing through the entire thickness of the section sex chromatin can be seen in about two-thirds of the nuclei, located at the periphery of the optical section of the nucleus as shown, or oriented in a different way.

Male specimens (Fig. 2 d). Nuclei of male epidermis do not contain a chromatin mass which is comparable in size to the sex chromatin of female cells. In the 50 specimens studied from 1 to 14 per cent of nuclei (average 5 per cent) showed a small chromatin mass at the nuclear membrane which may be sex chromatin, although it is difficult to be certain on this point. The evidence available to date indicates that the single X chromosome and the small Y chromosome of male nuclei fail to

form a chromatin mass of sufficient size to be distinguished from the general particulate chromatin in most cells. The nucleoli and particulate chromatin are the same in the two sexes. Typical nuclei of male epidermis are illustrated in Figure 2 d. This photomicrograph is characteristic of all focal planes through the section.

With some experience in this work there is no difficulty in sorting sections of skin correctly into male and female groups on the basis of nuclear morphology alone.

THE SEX CHROMATIN IN SKIN BIOPSIES OF HERMAPHRODITES

Severinghaus identified the XY chromosomes in developing germ cells of the testis in a case of male pseudohermaphroditism and Greene and associates (8) identified the XY chromosomes in similar cells in a case of true hermaphroditism. These seem to be the only previous cases in which the particular combination of sex chromosomes has been detected in intersexuality.

It has been our privilege to examine skin biopsies from 2 cases of hermaphroditism.

CASE 1. (Courtesy of Drs. W. A. Dafoe and E. A. Morgan.) This is a case of female pseudohermaphroditism with the adrenogenital syndrome. A skin biopsy was studied at the age of about 14 months. The nuclei of the malpighian layer showed a characteristic female morphology, the sex chromatin being visible in 75 per cent of nuclei in a 5 micron section. The sex chromatin was identical with that of the 50 sexually normal females studied earlier, with respect to size, position in the nucleus, and staining properties. This child, therefore, bears the female XX sex chromosome complex, as is to be expected from the clinical diagnosis. The essential points in the case history are as follows.

An enlarged clitoris, absence of labia minora and vaginal introitus, and labia majora rather larger than normal were noted at birth. The infant was registered as a girl. Signs of adrenal cortical insufficiency occurred at the age of 1 month and were brought under control with cortical extract.

The child was admitted to hospital at the age of about 14 months for a more thorough study of the genital system. The clitoris was ¾ of an inch in length. The urethral meatus was in the usual position for a female but no vaginal introitus could be found. Gonads could not be palpated in the labia or inguinal regions. At laparotomy the uterus, tubes, and ovaries appeared to be normally developed for a child of this age. A biopsy from one gonad showed typical ovarian structure on histologic examination. The adrenals seemed to be of normal size, in so far as this could be determined by palpation.

The adrenogenital syndrome accounts for a considerable proportion of female pseudohermaphrodites. Examination of a skin biopsy is a useful confirmatory diagnostic test and should largely eliminate the necessity of visualizing the internal genitalia by laparotomy in those cases which are still doubtful after urethroscopy and rectal examination. These cases present a serious problem as to management since the virilism is often progressive. The work of Wilkins and associates with cortisone offers some hope that a means of controlling the output of androgen from the hyperplastic adrenal cortex may be found, thus enabling the patient to adopt a life pattern in keeping with her chromosomal sex.

CASE 2. (Courtesy of Drs. W. Kerr and P. Crassweller.) This is probably a case of male pseudohermaphroditism, of the external type predominantly. True hermaphroditism cannot be rigorously excluded without extensive histologic examination of both gonads, although the chances are against such a diagnosis. A skin biopsy was studied when the patient was 24 years old. The morphology of the nuclei in the malpighian layer was indistinguishable from that of the 50 sexually normal males as described previously. A chromatin mass, which may be sex chromatin, was seen in only 4 per cent of nuclei. This individual, therefore, bears the male XY sex chromosomes. Summary of the case history follows.

Abnormal genitalia were noted at birth but the details are not known. The patient was raised as a boy. He was one of a family of 14 children and 1 sibling is said to have external genitalia similar to those of the patient. The patient has been studied in hospitals at distant centers and the complete records are not available. Bilateral mastectomy was performed at the age of 14 and an exploratory laparotomy was done at the age of 15. No ovaries or tubes were found but a testicular element was seen in the left inguinal canal. The following observations pertain to the most recent hospitalization.

The patient was admitted with complaints of tender swellings in the groins and monthly pelvic

distress lasting about 8 days, associated with hematuria. The patient was of indeterminate build with no important masculine or feminine characteristics. There was no growth of hair on the face and the distribution of the pubic hair was feminine. The phallus was small. The urethra opened at the base of the phallus and a shallow groove lined with mucous membrane extended from the urethral orifice to the perineal body. The urinary excretion of 17-ketosteroids was 16.6 milligrams in 24 hours.

No evidence of a prostate could be seen on cystoscopic examination. A longitudinal cleft on the enlarged verumontanum lead to a prostatic utricle about 2.5 centimeters long. The floor of this cavity showed fronds which appeared not unlike endometrial tissue. It was believed that this was the source of the periodic bleeding. The enlarged utricle was demonstrated by a urethrogram.

At a later date the gonad (grossly a normal testicle) was removed from the left inguinal region. The gonad on the right side was also exposed. It appeared to be a testicle and was replaced deeply in the inguinal canal after taking a biopsy. Microscopic examination showed the left gonad and the biopsy of the right gonad to consist of testis tissue. The patient is now receiving testosterone.

Although this patient has, we believe, male XY sex chromosomes there appears to have been a genetic factor, in view of the sibling with a similar anomaly, which directed sex differentiation along abnormal lines. If the influence of female sex hormones was involved we cannot say whether they originated in the fetal gonad, adrenal or in the placenta, or whether they may have been of maternal origin. The complex male pseudohermaphrodite group may prove especially profitable in the application of the skin biopsy test of chromosomal sex. The possibility that the nature of the gonads may not always correspond with the chromosomal sex must be entertained. It will be of equal interest to learn the type of sex chromosomes in the rare cases of true hermaphroditism.

DISCUSSION

Although the application of the skin biopsy technique to hermaphrodites is in a preliminary stage, it appears that chromosomal sex is as clear in somatic cell nuclei of hermaphrodites as it is in normal individuals. It is unnecessary to emphasize the possible importance of this observation in the investigative and practical aspects of the complex subject of hermaphroditism.

The term "chromosomal sex" has been used in this report rather than the more common expression "genetic sex." There is no serious objection to the alternative use of these terms when applied to individuals with normal sex development. In the present state of our knowledge it appears inadvisable to use the terms chromosomal sex and genetic sex interchangeably when referring to hermaphrodites. The indications are that it will be possible to establish whether an intersex patient has the female XX or the male XY sex chromosomes. However, this forward step is far removed from detecting the nature of the sex-influencing genes on these chromosomes or on the autosomes. It is evident from the familial incidence of hermaphroditism that the sex-influencing genes are inadequate for normal sex development in many cases. Our hope is that the chromosomal sex will prove to be a reliable indication of the *dominant* sex of the patient as a whole. Such a development would be the more valuable since the dominant sex could be detected *in infancy* by a relatively simple procedure.

Since many female pseudohermaphrodites and possibly a proportion of male pseudohermaphrodites are caused by endocrinologic dysfunction, the question arises as to whether the morphology of the sex chromatin is influenced by sex hormones. Unpublished observations in this laboratory indicate that this is not the case. One of us (M.A.G.) has demonstrated a sex difference in nuclear morphology in cat embryos before the stage of gonadal differentiation into testes or ovaries. Further, Mr. Hugh Lindsay was unable to alter the sex chromatin in neurons of the cat by orchectomy or oophorectomy in early life or by the administration of the opposite sex hormone to such animals. To the best of our knowledge the sex chromatin is a stable component of the nucleus whose morphology is not influenced by sex hormones. The morphology of the sex chromatin is believed, therefore, to be a reliable indication of chromosomal sex in hermaphrodites.

Certain remote possibilities are to be kept in mind in this work. For example, it is theoretically possible that a case of true hermaphroditism with an ovary on one side and a

testis on the other might be a gynandromorph, the term being used in the restricted sense of an individual in whom one side of the body is female, the other male. A bilateral biopsy would be indicated should such a possibility arise. It is also possible that some cases of hermaphroditism may be the result of a multiple combination of sex chromosomes, such as XXY. Such remote possibilities as these would seem to have no important bearing on the problem as it is now visualized.

In view of the unsatisfactory state of the subject of hermaphroditism it becomes a duty to establish the chromosomal sex in as large a series as possible. The authors wish, therefore, to make a special plea for the application of the skin biopsy technique in all cases of doubtful sex. It is especially important to do a skin biopsy test of chromosomal sex in the cases which have been described so thoroughly in the recent clinical literature. A sufficiently large series is required to permit a comparison of the chromosomal female hermaphrodites with the chromosomal male hermaphrodites. Such a comparison must include all the variables from the type of gonad to the psychosexual outlook of the patient. Only a thorough study of this nature, requiring the cooperation of many physicians, will permit an evaluation of the importance of chromosomal sex in hermaphroditism. Those who have faced the problem of treating these unfortunate patients will sympathize with the note of urgency in this appeal which reiterates a similar request made recently by Greenhill (9, p. 552).

SUMMARY

1. A study of skin specimens from 50 females and 50 males of normal sex development demonstrates a difference in nuclear structure, according to sex, in cells of the malpighian layer of the epidermis.

2. Nuclei of female specimens contain a mass of sex chromatin which is seldom seen in nuclei of male specimens. The sex chromatin is believed to be derived from heterochromatic parts of the sex chromosomes. The XX chromosomes of the female produce a chromatin mass sufficiently large to be identified, while the XY chromosomes of the male fail to produce a chromatin mass of sufficient size to be distinguished from the general particulate chromatin.

3. This method of detecting the chromosomal sex of an individual has been applied to 2 cases of hermaphroditism. One case proved to be a chromosomal female, the other a chromosomal male.

4. The extension of this study to other cases of intersexuality is urged in the hope of clarifying the complex problem of hermaphroditism. The potential importance of the skin biopsy technique lies in the possibility that it may prove to be a simple method of detecting the *dominant sex in infancy*, in cases of doubt.

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THE INCIDENCE OF CANCER WITH NIPPLE DISCHARGE AND THE RISK OF CANCER IN THE PRESENCE OF PAPILLARY DISEASE OF THE BREAST

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IF A patient with discharge from the nipple has a palpable mass in the breast, the discharge becomes of secondary diagnostic importance. The mass is explored as any lump in the breast would be. But if there is discharge without palpable mass, two questions arise: (1) Is it possible that there is cancer too small or too poorly defined to be felt? (2) If not cancer, is there a lesion present which indicates increased risk of development of cancer? Since the most common benign lesion responsible for discharge is papillary disease, the second question becomes that of the cancer-producing potential of papillary disease or of the breast tissue which has developed it. These two questions will be considered separately insofar as possible in this discussion.

One may read in the literature almost any grade of opinion about either of these questions. Some authors insist that cancer is never or almost never found in discharging breasts without palpable mass. Others state that cancer occurs in a small but significant number of cases of discharge (at least of serosanguineous character) although no mass can be felt.

Similarly the cancer-producing potential of papillary disease has been extensively debated for many years. Some regard the risk of development of cancer in the presence of papillary disease as moderate to very high. Others hold papillary disease to be quite innocent of risk. But while this debate is going on we are confronted with the very practical necessity of treating patients with nipple discharge and those with papillary disease.

The purpose of this paper is to set forth from our experience and from consideration of the literature, what we believe to be reasonable answers to these questions: (1) In the presence of nipple discharge with no mass palpable what is the likelihood of cancer being present? (2) Does or does not the woman with papillary disease run more risk of developing cancer than the average woman?

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Incidence of Cancer with Nipple Discharge

Our experience (to December, 1950) includes the observation of 190 patients with nipple discharge.

Character of the discharge has varied from clear watery fluid to yellowish, greenish, or dark brown, cloudy, milky or cheesy, or occasionally frankly bloody (Table I). Purulent discharges have not been included. The majority of these seen by us (in nonlactating breasts) have been dealt with in a separate report (15).

SECRETORY DISCHARGE

About one-sixth (32 of 190, Table I) had discharge either grossly milky or containing normal secretory elements microscopically—fat droplets and usually desquamated cells and debris. We have not seen cancer with such a discharge nor have we seen it as a forerunner of cancer. In 1 instance papillary cystadenoma has been found in a breast presenting such a secretory discharge. This patient was operated upon because of discovery of a palpable lump. In only 2 instances have we seen a milky discharge eventually come to contain blood.

In the nonlactating breast, duct mouths are normally closed by a plug of desquamated keratinized epithelium. If such a plug becomes dislodged—and the wonder is that they are not more often dislodged—secretion quite

TABLE I.—CHARACTER OF DISCHARGE AND ASSOCIATED PATHOLOGY

Character of discharge	No. of cases	Pathology found
Secretory (grossly milky or clear, yellow, green or brown with microscopic fat droplets)	32	1 papillary disease[1]
Serous (clear, yellow, green, brown). Never found to contain blood	55	3 papillary disease[1] 1 papillary disease[1] with associated cancer
Bloody (either at first examination or after observation with nonbloody discharge)	103	45 papillary disease 14 undifferentiated cancer 3 debatable cancer

[1]Operated upon because of presence of palpable lump.

normally present in the duct may appear at the surface. A secretory discharge (without mass) appears to mean no more than this and to require no treatment beyond occasional observation for change of character.

SEROUS, NONBLOODY DISCHARGE

Altogether 85 patients have been seen with serous discharge containing no blood at first examination. In 30 of these, at some time during observation blood was found in the discharge, and they, therefore, are included in the group with blood-containing discharge (Table I). In the remaining 55 patients in whose discharges blood was never demonstrated, 3 were found to have papillary disease and 1, papillary disease plus cancer—approximately 8 per cent with demonstrated papillary pathology. Womack believes that "any serous discharge from the breast, particularly in a patient beyond the age of 35, that contains no evidence of secretory material should be considered as plasma. This being so, it is usually evidence of ulceration somewhere in the duct system and is of considerable significance." It should be confessed that until the past few years we did not appreciate the importance of recording the presence or absence of secretory elements as well as of blood in discharges. It is probable, therefore, that a number of the 55 serous discharges in Table I actually belong in the secretory group. It appears that a serous discharge without fat must be regarded at least with more concern than a secretory one.

TABLE II.—LESIONS FOUND WITH BLOOD-CONTAINING DISCHARGE

	No. of cases
Cancer	
Undifferentiated 14	
Debatable[1] 3	17
Intraductal papilloma	36
Papillary cystadenoma	9
No lesion identified	10
Refused operation	31
Total	103

[1]See discussion of disagreement in pathologic interpretation, Part II.

BLOOD-CONTAINING DISCHARGE

Obviously something more than normal secretion is responsible for the presence of blood. It is worth emphasizing that patients' observation about the presence of blood is quite untrustworthy. Dark brown fluid, innocent of blood, may leave a stain on clothing closely resembling that of dried blood. The stain of a yellowish or even milky discharge will often be described as bloody. Only microscopic or chemical examination (we have used benzidine) can be relied upon.

Blood-containing discharge was presented by 103 patients. Almost one third of these (30 patients) have been seen when the discharge contained no blood. Sometimes blood has been found after a few days, sometimes only after many years of repeated examinations. Occasionally a discharge containing blood at one examination has been found subsequently free of blood.

In Table II are listed the lesions found in breasts with sanguineous discharge. It will be seen that bleeding was associated with benign papillary disease nearly 3 times as frequently as with cancer.

In 10 instances no lesion was found as a satisfactory explanation of bleeding (in 7 even after mastectomy). This is not to say that the breasts contained no simple cystic disease, sclerosing adenosis, mazoplasia, or sweat gland adenoma. But none of these ordinarily produce bleeding and we have assumed that some lesion not identified was responsible. Since bleeding may come from a papilloma no larger than a pinhead, it would not be remarkable if, without serial sections of the entire breast, one might sometimes be missed. We have not had the good fortune to find the small granulomas projecting into

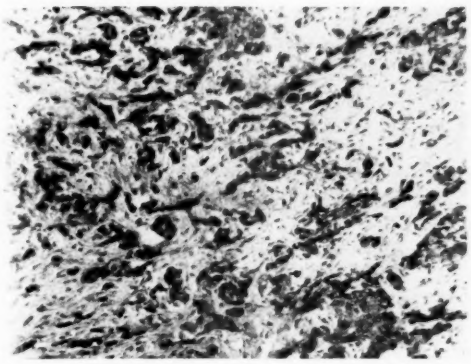

Fig. 1. Case 1. Carcinoma, not recognized grossly. ittle more than this one microscopic field was found.

Fig. 2. Case 1. Papillary disease from same slide as Figure 1.

ucts, described by Fitts, Maxwell, and Horn, certain cases of bloody discharge.

It was surprising that nearly 1 of 3 patients 1 of 103) with the frightening symptom of lood-containing discharge refused to have ything done about it. This is a particularly ifficult group to follow for obvious reasons, d we know with certainty the course be- nd 5 years in only 8 patients (12 have not t passed the 5 year period). So far as we ow, none have developed cancer. If one uld rely upon such a small number of cases e quite remarkable conclusion might be awn that the safest thing to do, in the pres- ce of nipple bleeding, is nothing!

INCIDENCE OF CANCER WITH BLOODY DISCHARGE WITH AND WITHOUT PALPABLE MASS

From Table III it will be seen that about of 6 patients (17 of 103) with bloody discharge had cancer or "debatable" cancer when first operated upon. Four of the 14 patients with cancer and 2 of the 3 with debatable cancer had no mass that we could feel. Stated with reference to the entire group of 103 patients with blood-containing discharge, 4 to 6 per cent, depending upon acceptance of the debatable group as malignant, had cancer without palpable mass.

The following case is illustrative of this group:

CASE 1. No. 13716, age 45 years. This patient had a history of discharge for 6 weeks which she thought contained blood from the appearance of a clothing stain. No discharge could be obtained at this examination. Five months later copious pure blood was seen by us and now, not a mass but a very diffuse, undefined irregular thickening extended in pie-shape from the areola to the lower inner margin of the breast. Pressure over this area at the areolar margin yielded discharge. This entire segment was removed. There was diffuse interstitial hemorrhage throughout but no individual duct could be found by multiple cross sections. Dr. Pearl Smith of the Children's Hospital made serial blocks of all the tissue removed and found on one slide only, the area shown in Figure 1. Figure 2 shows one of several areas of papillary disease also found in this and other sections. Radical operation was performed. No axillary metastases were found. The patient was well 13 years later.

EFFECTIVENESS OF METHODS OF FINDING INTRADUCTAL PAPILLOMAS RESPONSIBLE FOR NIPPLE BLEEDING

If it is accepted that the source of bleeding should be found and its nature determined and if it is desired to employ conservative local removal if the lesion proves to be benign, several methods of localization are available: palpation of a lump, transillumination, con-

TABLE III.—INCIDENCE OF CANCER WITH BLOODY DISCHARGE IN 103 PATIENTS WITH AND WITHOUT PALPABLE MASS

	With palpable mass	Without palpable mass	Total
Undifferentiated cancer	10	4	14
Debatable cancer	1	2	3
Totals	11	6	17

trast medium x-ray examination, exploration of the discharging duct with a probe as a guide, producing discharge by point pressure followed by wedge excision of the breast in the area indicated.

We have not used contrast medium roentgenograms for two reasons. First, instances of mastitis following injection of radio-opaque material have been reported. Second, as will be mentioned later, while multiple papillomas do occur in the same duct, they are even more likely to be in multiple ducts, sometimes widely separated, and these would be easily missed by this method.

Transillumination has been of small value. We were able to locate only 4 intraductal papillomas by a definite shadow. In 8 cases we could not be sure whether we were seeing a faint shadow or not. In 2 we thought we saw a shadow where the papilloma proved not to be, and in all the rest no shadow was seen. This does not seem too remarkable since no shadow is cast by the papilloma itself. Only if sufficient blood is collected in a duct dilated about a papilloma will a shadow be cast.

Palpation of an intraductal papilloma as a lump has been almost equally unsatisfactory. Fourteen could be distinctly felt. In 17 there was a questionable lump. This has usually meant that, after determining the location of the bleeding duct by point pressure, one could then feel some irregularity along its course which proved to be where the papilloma was found. Nothing could be felt in the other cases even with this lead. Again this is not surprising because of the small size of many papillomas and because their texture is not greatly different from that of surrounding breast tissue.

Babcock first offered the ingenious suggestion of working a small probe (such as the blunt end of a fine cambric or milliner's needle) into the discharging duct. This furnishes an excellent guide and it is gratifying to see a pedunculated papilloma extrude as the duct is split over the probe. The needle can usually be introduced 4 to 6 centimeters to the main duct branches, and often deeper. Before concluding exploration it does no harm to split the duct completely to its mouth at the nipple surface. One stitch accurately placed at the nipple base is sufficient to restore its configuration. No stitches are needed on the surface of the nipple. The scar of healing on the nipple is minimal if not actually invisible. Several times papillomas have been found in the nipple itself or in its base. These could not be, or at least were not, found by palpation or transillumination. Such a location should be particularly considered when discharge is obtained only by milking the nipple and not by point pressure over or around the areola. Probe exploration was tried in 25 cases. Papillomas were found in 12, not found in 8, and in 5 we were unable to probe the duct.

Failing to find a papilloma by exploring the duct over a probe (or as an elective procedure in the first place), wedge excision was done in 25 instances with discovery of papilloma in 20.

It is apparent that, in our hands, none of these methods has been uniformly successful.

MULTIPLE INTRADUCTAL PAPILLOMAS

Of 49 patients proved to have intraductal papillomas, multiple lesions were demonstrated in 14 (28 per cent). In 11 they were in multiple ducts, sometimes widely separated, even in opposite quadrants of the breast. Four such instances were found only at second operation for recurring discharge.

It appears that the number of cases in which papillomas are found to be multiple depends largely on the amount of breast removed and carefully examined. Thus Chester and Bell found the incidence of multiple papillomas to be twice as great when mastectomy had been done as when only a wedge of tissue had been excised. Reports of multiplicity run as high as 80 per cent.

BILATERAL PAPILLARY DISEASE

The relatively common multiplicity of papillary lesions in one breast leads naturally to inquiry about the frequency of bilateral occurrence. It might well be thought that, if papillary disease is due to hormonal influence or to some inherently increased growth potential of an individual's breast epithelium, bilateral involvement would be common. Our experience does not prove this to be true. We have seen papillary disease demonstrated

laterally in only 2 patients. Bilateral blood-ontaining discharge is equally uncommon hile bilateral secretory discharge is observed uch more often.

SMEAR EXAMINATIONS

Our experience with smear examinations of pple discharges has so far been too limited permit conclusions to be drawn about their alue. When there is blood in a discharge, near examination will, it seems to us, neither viate the need of exploration nor help ate the source of bleeding. It is perhaps in e presence of blood-free but nonsecretory scharges that smears may prove of help.[1] or an extensive study of smear examinations nipple discharges reference is made to the ork of Jackson and Severance.

THE RISK OF CANCER IN THE PRESENCE OF PAPILLARY DISEASE

As mentioned at the beginning of this per, for many years there has been a wide vergence of opinion among students of east disease about the risk of cancer offered the presence of papillary disease of the east. It is perhaps in order to reflect on the obable reasons for this conflict, several of hich present themselves.

REASONS FOR DIVERGENCE OF OPINION

Failure to distinguish sharply in statistical udies between the symptom of discharge and the esence of demonstrated papillary disease. If, r example, in a considerable number of easts presenting serosanguineous discharge ncers are found, it can by no means be sumed that benign papillary disease pre-ded the cancers as a cause of discharge and at, therefore, papillary disease has a high precancerous" potential.

Statistical inadequacy. Most studies of both ipple discharge and papillary disease have een based on 100 to 300 cases, more or less. When, for example, from such total numbers those which have been proved to be papillary disease by local removal of a lesion are segregated for follow-up study, this number may well be so small that percentage deductions are subject to wide chance of error. If one is to determine whether there is or is not an increase of cancer risk from, possibly 0.5 per cent to 1.5 per cent, a total number of 70 or 80 cases is manifestly too small. And yet this increase would represent trebling the average risk which would be of high importance to a patient.

Our experience reported here is subject to this same criticism. Yet the very justification for reporting another study is the desirability of having recorded as much observation as possible so that some concept of what is average experience may be obtained.

Inadequacy of follow-up. While the customary 5 year period is a practically useful one for study of cancer treatment it is not sufficient for study of cancer risk. Having survived, free of apparent disease, the standard 5 year period after operation for cancer of the breast, a woman is probably less likely to develop recurrence in the next 5 years and still less in the third. If, however, she has in her breast tissue some factor which increases the risk of developing cancer, her risk should be just as great in the second and third 5 year periods as in the first. In fact, in relatively younger women it should increase with advancing age. Only a lifetime follow-up would be complete and this is an unattainable ideal. In studying the instant problem, the workable compromise which must be made is that suggested by Warren, Chester and Bell, and others of comparing the incidence of cancer in breasts from which papillary disease has been removed locally over a practical period of 5 to 10 years with the calculated average incidence of breast cancer in the same period of time, either in the general adult female population or, better, if the number of cases studied permits, in women of comparable age groups.

Disagreement in pathologic interpretation. Papillary disease of the breast presents histologic pictures varying from those which are certainly benign to others unquestionably malignant,[1] sometimes in the same breast or even actually in the same tumor mass. Between these extremes many pictures offer no small

[1] There is a small group of pure carcinomas of polypoid or papillary type, some within well defined cystic cavities. We have seen none of these associated with or following benign papillary disease in the same breast and they have, therefore, not been included since this is a study of the relationship of benign papillary disease to cancer.

Fig. 3. Case 2. Longitudinal section of intraductal papilloma. Neighboring duct sections also contain papilloma.

difficulty in interpretation and are subject to diverse opinions among experienced pathologists. It is quite probable that some authors who report a high percentage of malignant change in benign papillary disease are classifying as cancer some lesions which others would call benign or, at most, equivocal. Such differences in pathologic interpretation doubtless also help to explain the wide variations in reported incidence of cancer in the presence of discharge, from very low to as high as 50 per cent.

In reporting our experience it is the intent to distinguish (as in Table II) between undifferentiated, unquestionably invasive cancer (medullary, simplex, scirrhous, Fig. 1) upon which we are confident there would be no disagreement and a debatable group (usually intraductal or with questionable areas of invasion) which we think are malignant but which others might doubt or think benign.

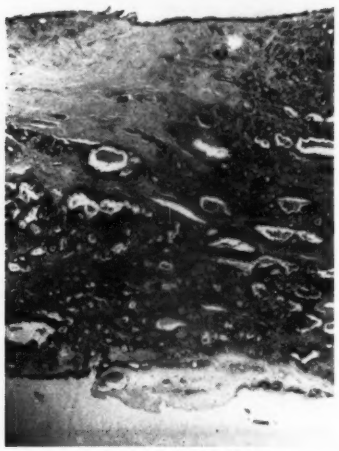

Fig. 4. Case 2. Section from midportion of papilloma shown in Figure 3.

We have called these "debatable" rather than "borderline," the more commonly used term. Presumably there is no such thing as borderline cancer (but only borderline pathologists). Unless the acquisition of malignant properties—distortion of cell form and metabolism, loss of control of functional arrangement, capacity to invade and metastasize—is in stages and unless this process, once begun, may be reversible, then a single cell, once it is no longer benign, is as malignant as a million cells. And it is obvious that before cells can invade outside normal epithelial boundaries they must have acquired the capacity to do so while still within boundaries. This property is, of course, well recognized in comedo carcinoma before the pattern of scirrhous carcinoma has developed. Some of us find it difficult on occasion to be categorically sure whether the change to malignancy has actually occurred and the pictures presented will, we think, inevitably give rise to disagreement. As a matter of fact, more than once we have restudied sections after several months and disagreed with ourselves.

Listed in Table II is a small group of debatable cancers. We think they are actually malignant and so cannot properly include them among the benign papillary lesions. They have been segregated in order to avoid weighting the incidence of unquestioned cancer and where, in this paper, the word cancer is used without qualification it applies only to what we regard as unequivocally malignant lesions. In fact the cancers reported hereafter, as found with papillary disease or arising subsequent to local removal of papillary disease, are all undifferentiated and none fall in our debatable group.

Problem in semantics. The very term "papillary disease" presents a problem in semantics. Without sitting at the same microscope it may well be difficult for one student to be sure what another means by papillary disease. Does the term include epithelial proliferation completely filling duct lumina without actual stalk or polypoid formation? Per-

haps a term like "intracanalicular" or "intracystic epithelial hyperplasia" would be a better one. Does it include the very small areas of proliferation found only incidentally on microscopic examination as occasionally in breast tissue surrounding simple cysts? Does it include the almost ubiquitous cystic spaces lined by pink-staining epithelium in finely papillary form generally regarded as sweat gland adenoma?

For the purposes of this study we have considered as papillary disease only lesions of such extent as to constitute grossly recognizable masses or those presenting widespread and striking microscopic changes. The fairly frequent instances of local and minimal proliferative changes found only incidentally by the microscope have not been included. Sweat gland adenoma has not been included.

For study of the question of the risk of cancer in the presence of papillary disease, there have been added to the 45 intraductal papillomas and papillary cystadenomas found with sanguineous discharge (Table II) an additional group of 34 similar lesions discovered as palpable lumps without discharge (Table IV).

ESTIMATE OF CANCER PRODUCING POTENTIAL

There are several possible lines of evidence leading to some estimate of the cancer producing potential, if any, of papillary disease of the breast containing papillary disease.

Cancer in close association with or as apparent extension of papillary disease. Classic examples are the 2 cases reported by Greenough and Simmons. Of the 79 cases of papillary disease listed in Table IV, 6 presented such association. The following cases are illustrative:

CASE 2. No. 10282, age 45 years. When first seen the patient had a clear watery discharge of 6 weeks' duration. Two months later she was again seen with clear discharge. Six months later she insisted that she had seen bright red blood. Presence of blood could not be confirmed then or a month later by microscopic examination. Three years after first observation there was still a clear discharge but there was now a very small erosion in a recess in the nipple. Because of the erosion, as well as her insistence that she had seen fresh blood, exploration was done although still no mass could be felt.

The discharging duct was explored over a probe and an intraductal papilloma 2 centimeters long with narrow base was found 5 centimeters from the nipple. At its base a 5 millimeter, hard, sharply defined mass with gross characteristics of carcinoma was found. Frozen section confirmed the diagnosis and immediate radical operation was performed. Longitudinal section of the papilloma in very low power is shown in Figure 3, a section from the midportion of the papilloma, interpreted as benign, in ordinary low power in Figure 4. Figure 5 is from the small cancer at the base of the papilloma. No metastases were found in axillary nodes. The patient was well 13 years later.

Fig. 5. Case 2. Carcinoma at base of papilloma shown in Figure 3.

CASE 3. No. 18995, age 69 years. Papillary cystadenoma, 1 centimeter in diameter, was discovered as a palpable lump. Figure 6 shows a typical area of the papillary cystadenoma comprising most of the mass. Figure 7 shows a small edge of papillary disease and, adjacent to it, although no direct continuity was demonstrated, scirrhous carcinoma. The cancer was not apparent grossly and was discovered only in frozen section. No metastases were found in axillary nodes. The patient was well 6 years later.

CASE 4. No. 21837, age 36 years. A palpable lump first observed 3 weeks before examination was found to be an unencapsulated papillary cystadenoma, 2 centimeters in diameter. One area was grossly suggestive of carcinoma and this diagnosis was confirmed by frozen section. Figures 8, 9, and 10 are from contiguous areas in that order. Other areas of benign papillary cystadenoma were found in the breast well away from the explored lump. No

TABLE IV.—TOTAL CASES OF PAPILLARY DISEASE

	With discharge	Without discharge (palpable lumps)	Total
Intraductal papillomas	36	13	49
Papillary cystadenomas	9	21	30
Totals	45	34	79

Fig. 6. Case 3. Typical area of extensive papillary cystadenoma.

axillary metastases were found. The patient was well 3 years later (1951).

A similar instance of papillary disease displaying various stages of atypism from benign to frankly malignant is reported in detail by Foote and Stewart. In their case the microscopic pictures of successive degrees of change from benign to malignant were taken from separate areas of a breast. In Case 4 the 3 photomicrographs are of sections from the same lump.

What is the probability that these cases of cancer in close association with benign papillary disease represent only coincidence? Our records contain 79 cases of papillary disease (Table IV). In 6 of these, cancers were found in association. We also have records of 335 single or multiple cysts of simple "blue domed" type occurring as clinical lumps. With 3 of these, cancer was found in close association. The comparison thus is as follows:

	Total	Associated with cancer	Per cent
Papillary masses	79	6	7
Simple cyst masses	335	3	1

Cancer with papillary disease elsewhere in same breast. Less persuasive but at least circumstantial evidence would be the occurrence of cancer with papillary disease elsewhere in the same breast. Foote and Stewart, for example, although they found papillary disease without atypism no more frequently, found atypical papillary disease five times more often in cancerous than in noncancerous breasts (see also our Cases 1 and 5). Estes and Phillips found 6 coexisting cancers in 87 instances of papilloma.

Discharge for several years before discovery of cancer. Still less conclusive but only suggestive evidence is offered by case histories of discharge for several years before eventual discovery of cancer. Hinchey, for example, reports 1 patient with a discharge for 3 years and 1 for 4 years before cancer was found. Donnelly records a history of observed discharge and no mass for 10 years until axillary metastasis led to the diagnosis of cancer.

As already stated, such histories by no means offer conclusive evidence that benign papillomas preceded the cancers, but it must be assumed either that the cancers existed unusually long before discovery, in spite of search for palpable lumps, or that something causing discharge existed before cancer and, again, the most common nonmalignant lesion producing serosanguineous discharge is papilloma. Case 2 seems to be a fairly convincing example of such a sequence. The papilloma which had apparently been responsible for discharge for 3 years was still present at exploration. It seems highly unlikely that a cancer only 5 millimeters in diameter had been present as long as 3 years. In another of our cases discharge had been observed for 10 years before cancer was found. It is perhaps not impossible

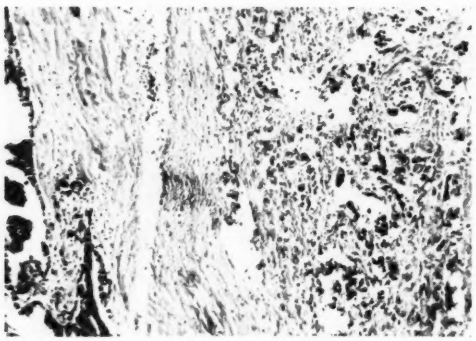

Fig. 7. Case 3. At left an edge of papillary cystadenoma; at right, scirrhous carcinoma, not recognized grossly, found by frozen section.

hat in some instances the cancers, by the me they were found, had destroyed papil- mas originally responsible for discharge.

Incidence of cancer after local removal of pillary disease. For practical clinical pur- ses the most important consideration is the elihood of development of cancer after local moval of papillary lesions. If this occurs th significant frequency it must be assumed ther that other papillary lesions with precan- rous potential were left in the breasts or that easts which produce papillary disease have some way an inherently greater than aver- e cancer-producing potential themselves.

Haagensen, Stout, and Phillips, Estes and hillips, and Campbell report that no patients ve been known to have developed cancer ter local removal of papillary disease. On e other hand, Geschickter found cancer ter in 3 of 54 patients, Warren in 3 of 21, onnelly in 3 of 15 (plus 3 intraductal carci- mas—possibly debatable). Our experience set forth in Table V.

Thirty-four intraductal papillomas (of 49 und—Table IV) and 23 papillary cystade- mas (of 30) were locally removed, altogether local excisions of papillary lesions. In 6 of ese, cancer developed in the same breast 2, 2, 3, 4, and 5 years later (and 2 in the posite breast 2 and 8 years later). The ages the 8 patients who developed cancer within ch relatively few years are interesting: 29, 36, 39, 42, 44, 46, and 51 years at the time of discovery of cancer. Case histories of 3 of these are presented.

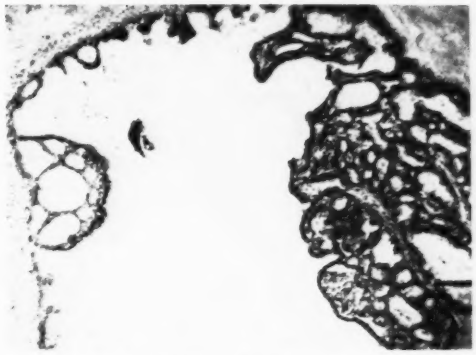

Fig. 8. Case 4. Papillary cystadenoma.

CASE 5. No. 22179, age 44 years. Seven months before our first observation local excision had been done elsewhere of a lump 3 or 4 centimeters above the nipple, presumably responsible for serosanguineous discharge, with finding of multiple intraductal papillomas. There was now recurrence of discharge containing blood. She refused mastectomy and the discharging duct, this time extending in the opposite direction into the lower outer quadrant of the breast, was explored over a probe. A loose body the size of a grain of rice was picked out of the duct. In a section of this there could be distinguished the pattern of papilloma which had apparently spontaneously detached from its pedicle. In the breast about the explored duct other microscopic areas of papillary overgrowth were found and she was again urged to accept mastectomy but still refused. Sixteen months later she appeared with a small mass, this

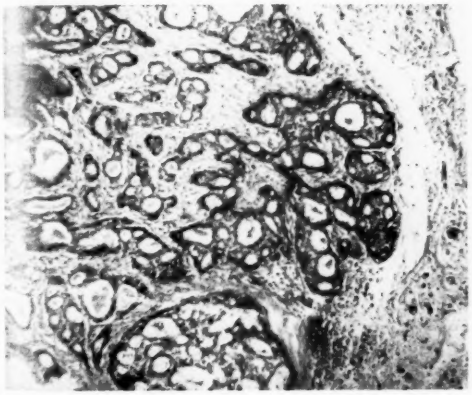

Fig. 9. Case 4. Debatable cancer, from same mass as Figure 8.

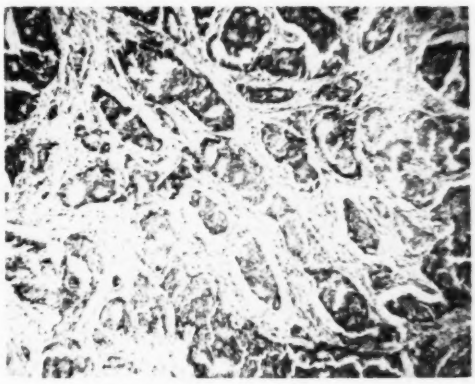

Fig. 10. Case 4. Cancer, from same mass as Figures 8 and 9.

TABLE V.—INCIDENCE OF CANCER AFTER LOCAL REMOVAL OF PAPILLARY DISEASE

	Total local removals	Developed cancer later	
		Same breast	Opposite breast
Intraductal papilloma	34	2	1
Papillary cystadenoma	23	4	1
Totals	57	6[1]	2[1]

[1]All undifferentiated cancer. Three of the 6 in the same breast and 1 of the 2 in the opposite breast are dead of metastases.

time in the upper inner quadrant about 4 centimeters away from the scar of original operation. It proved to be scirrhous carcinoma. Multiple areas of papillary disease were found in sections taken at random through the breast. One is shown in Figure 11.

No metastases were seen in axillary nodes but within a year she died of bone and visceral metastases.

CASE 6. No. 10364, age 46 years. A pedunculated intraductal papilloma was removed from a bleeding duct just outside of and below the areola. She was next seen 4 years later with cancer of the upper outer quadrant, inoperable because of distant metastases. She died within the year. This was a forthright, intelligent woman yet the metastases were already demonstrable when the cancer lump was found.

CASE 7. No. 10139, age 27 years. This patient had had a yellow discharge for 6 months which contained red blood cells. There was poorly defined lumpiness throughout the breast. The one area which seemed more definite than others was excised and found to be papillary cystadenoma. Blood-containing discharge continued and mastectomy was suggested but refused. Two years later she was next seen with enlarged axillary nodes proved by biopsy to be carcinoma. She died within a year.

Considering only those instances of cancer arising in the same breast (Table V), 6 of 57 patients or about 1 in 10 developed cancer within 5 years after local removal of papillary disease. As already mentioned, percentage deductions drawn from such a small number of cases are subject to error. Still the difference between this incidence (1 in 10) and the expected incidence of breast cancer in women of roughly comparable ages, 35 to 45 years—of the order of 0.5 to 1.0 per cent[1] in a 10 year period—may well arouse apprehension. And if to these cancers, arising subsequent to removal of papillary disease, are added the instances in which papillary disease and cancer were found in close association at first operation (Cases 2, 3, and 4), the suggestion of some relationship between papillary disease and cancer seems to us inescapable.

Again it may be appropriate to compare this incidence of 1 in 10 after local removal of papillary disease with the incidence of cancer later in breasts which have presented clinical lumps of simple cystic disease. Of 335 patients who have had clinical lumps of simple cystic disease removed or aspirated, 6 have developed cancer later in the same breast after 1½, 2, 10, 13, 15, and 18 years at ages 35, 44, 46, 50, 57, and 60 years. The comparison is as follows:

	Total	Developed cancer later	Per cent
Papillary masses	79	6	7.5
Simple cystic masses	335	6	1.8

ATYPISM OF CELLS IN PAPILLARY DISEASE

It would be an important observation indeed if the degree of atypism found in locally removed papillary disease could furnish a reliable index of the likelihood of cancer developing later in the same breast. Foote and Stewart approached this problem from the opposite direction, so to speak, by studying breasts removed for cancer and breasts removed for other reasons. They define atypism as indicating disturbance of cell uniformity including the usual traits such as altered stainability, variation in size and/or shape, and loss of polarity. They found typical papillary disease no more frequently in cancerous than in noncancerous breasts but atypical papillary disease 5 times as frequently in breasts with cancer as in those without.

We have restudied our cases of benign papillary disease for pleomorphism, variations in staining, piling of cells, and occurrence or absence of secondary papillary changes in the walls of ducts or cysts away from the main papilloma. Only in a very general way is it possible to say that a substantial degree of such alterations appears more likely to be

[1]Dublin has calculated that the chance per 1,000 white females of acquiring cancer of the breast in the next 10 years is 2.8 (0.28 per cent) at age 35 years and 5.5 (0.55 per cent) at 45. These figures of *onset* are based on mortality statistics corrected by a factor of 4 years for average duration of life from onset to death.

It is to be hoped that some breast cancers are cured and never reach mortality statistics for this disease. If 1 of every 2 breast cancers seen, operable and inoperable, were cured we would be doing very well indeed. Thus doubling the above figures to 0.56 per cent at 35 and 1.1 per cent at 45 years of age should provide a very liberal estimate of average incidence.

found in papillary disease associated with or followed by cancer.

Discussion

In our experience from 4 to 6 per cent of women with blood-containing nipple discharge have been found to have cancer without palpable mass. If the symptom of nipple bleeding can lead to discovery of even a few very small and presumably very early cancers it is a valuable symptom to these patients for the cure rate should be high. Discovery and removal of the early lesions in this small group has been a rewarding experience for us.

This study has not been concerned with the mechanisms, presumably hormonal, responsible for the development of papillary disease or with the relationship of papillary disease to the other protean manifestations of pathology included in the broad term "chronic cystic mastitis." No attempt has been made to evaluate the risk of cancer presented by any or all of the other manifestations of cystic disease as compared to that of the "normal breast." Studies in these fields have been made by many others including Warren and Foote and Stewart whose reports have already been mentioned.

It need hardly be argued, however, that the epithelial overgrowth of papillary disease is a quite different process from the epithelial atrophy characteristic of the simple cyst. This study has been concerned with the problems presented to the clinician by the patient whose symptoms—nipple discharge or palpable lump—has led to the discovery of papillary disease. Does this particular manifestation of epithelial change in the breast indicate increased risk of cancer over that of the woman who has had no such symptoms or who has had clinically demonstrated simple cystic disease?

Of 79 cases of papillary disease 6 have been found to have cancer in close association. Of 57 patients who have had local removal of papillary disease 6 have developed cancer in the same breast within from 2 to 5 years.

We are quite prepared to believe that these figures may present a distorted picture because of the relatively small number of cases observed. A more accurate one might be obtained with several hundred from which to draw percentage deductions. Still, from this experience and from the experience of other authors, the conclusion seems inescapable that there is some relationship between papillary disease of the breast and cancer and that, while the risk may not be as great as our small series suggests, nevertheless, it is increased over that of the average woman of similar age.

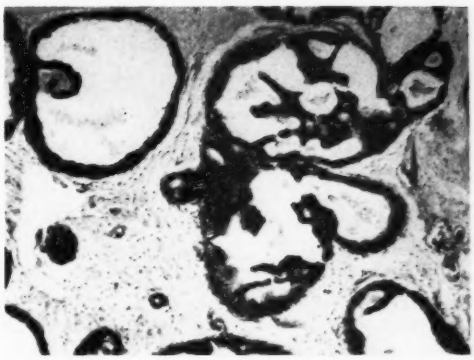

Fig. 11. Case 5. One of multiple scattered areas of papillary disease.

Once a woman has had cancer of the breast the possibility of recurrence still remains even after many years of apparent freedom from disease. Even the best of 5 year, to say nothing of life-time, cure rates is none too good. The average risk of developing cancer of the breast is high enough. If we can recognize a precancerous lesion which raises this risk even moderately it deserves, to say the least, serious attention.

We believe that the woman of cancer age, 40 or beyond, who has a blood-containing discharge, and so either cancer or presumably papillary disease, would be well advised to accept mastectomy in view of the frequency of multiple papillary lesions and the uncertainty of their discovery. Even younger women who have been proved to have multiple papillary lesions, especially if these are in separate areas of the breast (as in Case 5) and certainly if they have displayed atypism of papillary epithelium, should accept mastectomy.

There appears to be, however, no valid reason for not allowing an intelligent patient to accept some burden of decision. It seems

fair to inform her that there is disagreement between experienced students of breast disease about the relationship of papillary disease to cancer and that, while we share with others the opinion that its presence indicates increased risk, there is good authority for regarding it as innocuous. If she is willing to run, what we think is, appreciable increase of risk for the sake of keeping her breast the decision should be hers to make.

In any event, exploration for the source of bleeding is in order.

As already mentioned, it would seem logical that if the tissue of one breast produces papillary disease, very commonly in multiple areas, that of the other breast might be expected to behave similarly. Also if the presence of papillary disease in an individual's breast tissue indicates greater than average tendency to produce cancer, the breast tissue on both sides might be expected to display the same increased tendency.

Studies on much larger numbers of patients may yet show this to be true, but for the present there does not appear to be proof. If one is prepared to advise removal of the breast in which papillary disease has been found, he cannot on good grounds advocate removal of the opposite breast with equal force, though in 2 of our cases, after the fact, we sincerely wished we had been able to do so.

Conclusions

1. A secretory discharge, either grossly milky or containing secretory elements microscopically, appears to be of little significance and to require no more than observation for change of character.

2. A serous discharge without secretory elements will, in one third or more of the cases, be found at some time to contain blood. Such a discharge, therefore, carries significance potentially similar to that of one containing blood.

3. In the presence of blood-containing discharge without palpable lump the chance of cancer being present is about 1 in 20 to 1 in 25. For this reason alone the source of bleeding should be found and its nature determined.

4. If cancer is not present, probably bleeding is coming from papillary disease.

5. There is wide and apparently irreconcilable disagreement about the relationship of papillary disease to the development of cancer. Our conviction is that its presence indicates risk appreciably above average

6. Of the methods of locating and locally removing a single lesion of papillary disease in the absence of palpable lump none are uniformly successful, and if such a lesion is found the chance of leaving other undiscovered lesions elsewhere in the breast is considerable.

7. For these reasons the woman beyond 40 with blood-containing discharge or demonstrated papillary disease is advised to consider the acceptance of mastectomy (extended to radical operation if cancer is discovered). Even younger women with multiple lesions are offered similar advice.

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CARCINOID TUMORS

A Clinical and Pathologic Study of 27 Cases

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CARCINOID tumors are primary neoplasms of the gastrointestinal tract which may occur at any point from the cardia of the stomach to the rectum. The designation carcinoid was chosen by Oberndorfer in 1907 because of his belief that the lesions were benign. Recent reports tend to emphasize the malignant potential of these tumors.

Metastases were found in 10.2 per cent of rectal carcinoids reviewed by Tavenner, Deacon, and Peale; in 24.9 per cent of 237 small bowel carcinoids reviewed by Ariel; and 37.9 per cent of 332 nonappendiceal carcinoids reviewed by Ritchie and Stafford. Dockerty and Ashburn analyzed 30 cases of carcinoids of the ileum which presented gross and microscopic evidence of extension and advocated the term grade I adenocarcinoma (carcinoids) for these lesions to emphasize their malignancy. The term argentaffin-cell tumor, introduced by Masson, was based on the cells' affinity for silver stains.

This review deals with carcinoid tumors encountered at Hines Veterans Administration Hospital, Hines, Illinois, and attempts to correlate the microscopic appearance and clinical course, and, furthermore, to formulate the treatment.

Of the 27 cases studied, in 3 the tumors were duodenal, in 4 ileal, in 2 they were in a Meckel's diverticulum, in 3 they were cecal, in 9 rectal, and in 5 appendiceal. In 1 case the tumor was so extensive that the primary site could not be determined. Each of these groups is described and discussed.

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Three duodenal carcinoids were found:

CASE 1. No. 277,746. This 62 year old negro was hospitalized in December, 1948, at which time an anterior resection was performed for adenocarcinoma of the sigmoid colon. He returned to the hospital in October 1950, with the symptoms and findings of a high partial small bowel obstruction. An upper gastrointestinal x-ray study revealed a filling defect in the first portion of the duodenal bulb. At laparotomy a tumor 1.2 by 0.6 centimeter in size was found just distal to the pyloric region on the anterosuperior surface of the duodenum. On gross inspection it appeared to be entirely submucosal and did not appear to infiltrate the muscular layer. The overlying mucosa appeared to be normal. There was no evidence of metastatic spread. The tumor with a full thickness cuff of duodenum was resected and an anterior gastroenterostomy established. The postoperative course was uneventful, and when last seen, 21 months later, he was asymptomatic and without evidence of recurrence.

Microsection showed the entire duodenal wall from mucosa to serosa infiltrated with small carcinoid cells, uniform in size, without glandular formation. No abnormal mitoses were noted.

CASE 2. No. 306,563. A 61 year old white male on admission complained of nausea, vomiting, diarrhea, jaundice, and a 5 pound weight loss during the preceding 2 weeks. Obvious jaundice was present, laboratory studies were compatible with obstructive jaundice, and x-ray observations revealed a filling defect in the duodenum. At operation a firm, nodular mass was localized at the ampulla of Vater. This was excised transduodenally with closure of the mucosal defect and a T tube was placed in the common duct. The postoperative course was complicated by a wound dehiscence which was repaired and by urinary retention which required transurethral resection 2 months after the original operation. His jaundice cleared following surgery and he was asymptomatic, free of jaundice, and gaining weight in October 1951, one year postoperatively. In May 1952, jaundice and weight loss recurred and the patient expired in July 1952. Autopsy disclosed local recurrence of the carcinoid with associated obstruction of the common duct and invasion of the adjacent pancreas (Fig. 1) but there was no evidence of distant metastases. Death was caused by liver insufficiency secondary to common duct obstruction.

Fig. 1. Recurrence of carcinoid at the ampulla of Vater with common duct obstruction.

Microsection showed an ulcerated surface of carcinoid cell masses with remnants of glandular structure of the mucosal glands (Fig. 2). In the autopsy specimens the common bile duct and pancreatic ducts were surrounded by carcinoid cells. Masses and cords of tumor cells penetrated the muscular coat of the duodenum and invaded the serosa. The nuclei showed changes in size and staining quality and some were bizarre in shape (Fig. 3). Acinar structures lined by columnar cells with tumor masses growing from their walls were frequent. A reddish stained coagulum occupied the lumen of these glands in some instances. Cells on the surface, near the ulcerated area, showed definite malignant changes.

CASE 3. No. 289,511. On admission, February 1949, this 57 year old negro complained of weakness and weight loss. Exploration disclosed that the liver contained tumor nodules for which no primary lesion was found. He expired in a cachectic state in February 1951, 24 months after admission.

The liver weighed 7,385 grams at autopsy and was almost entirely replaced by cauliflower-like tumor masses, ranging from a few millimeters to 12 centimeters in size. Enlarged nodes were present about the celiac axis but no other foci of malignancy were uncovered. A rounded depression 0.5 centimeter in diameter was observed in the first portion of the duodenum 2 centimeters from the pylorus which on microsection was carcinoid. Histologic studies revealed carcinoid in the duodenum, celiac lymph nodes, and liver. The earlier liver biopsy was a carcinoid similar to the tumor found at autopsy (Figs. 4, 5, 6, 7, and 8).

Carcinoid of the duodenum is seen as a small nodule or polyp varying from 0.5 to 3 centimeters in size, it is usually asymptomatic and is found incidentally in the course of x-ray study of the stomach or gallbladder. It appears as a rounded filling defect in the first part of the duodenum (Fig. 9). If it is located at the ampulla of Vater, jaundice may occur when the tumor is small in size because of common duct obstruction as reported by Brunschwig and Childs. Our patients averaged 60 years of age, 2 were negro, 1 was white, all were male. Microscopically, the tumor in 1 of the cases discussed was entirely submucosal and did not invade the muscularis. This patient has been free of evidence of recurrence for 21 months. The 2 patients whose tumors appeared malignant microscopically died of carcinoids. Superficial ulceration was noted once, while in 2 instances carcinoid cells had reached the serosa. It appears, therefore, that carcinoid in the duodenum has a marked malignant potential which appears to be correlated with the microscopic appearance.

We believe that the treatment of choice for duodenal carcinoid is local resection of the tumor with a cuff of normal tissue. One patient so treated is well and without evidence of recurrence 21 months postoperatively. Hannan reported freedom from recurrence for 24 and 27 months in cases treated similarly. Brunschwig performed a pancreaticoduodenectomy for a carcinoid in this location. The patient was well 15 months postoperatively. Warren and Coyle reported a patient who expired with osseous metastases 4 years and 8 months after pancreaticoduodenectomy.

Four ileal carcinoids were found:

CASE 4. No. 301,583. This 56 year old white male was admitted with a 3 months' history of rectal bleeding. Examination revealed a nodular growth at 9 centimeters which was reported as adenocarcinoma on biopsy. In November 1951, a Miles abdominoperineal resection was performed. At surgery a contracted, firm, yellowish nodule 1 by 1.5 by 0.8 centimeter in size was found in the ileum 25 centimeters from the ileocecal valve. Tumor appeared on the serosal surface on gross inspection and there was constriction of the bowel lumen. There was no evidence of extension into the mesentery or regional nodes. Five centimeters of intestine were resected and an end-to-end anastomosis accomplished. The tumor in the rectum was found to be an adenocarcinoma; the ileal mass was a carcinoid.

Microsection showed uniform carcinoid cells with rare mitoses. However, it had penetrated to the serosa and carcinoid cells were found in the lym-

tic spaces. The hospital course was uneventful, and when seen 6 months after surgery the patient was asymptomatic. This patient also had a basal cell carcinoma in the right preauricular area.

CASE 5. No. 108,542. In November 1940, this year old white male had abdominal exploration with a diagnosis of "chronic appendicitis." He had symptoms in the right lower quadrant for 13 rs. At surgery a pedunculated tumor 1.0 centiter in diameter was found in the terminal ileum removed locally. Postoperative x-ray studies negative for lesions of the intestine.

Microsection showed the entire thickness of the stine to be invaded by carcinoid cells in cords sheets. The cells were uniform in size and no oses were seen. Twelve years after surgery, in rch 1952, he was asymptomatic.

CASE 6. No. 127,067. This 43 year old white had an emergency laparotomy in May 1942 acute bowel obstruction complicated by perfora-. The ileum was found studded with at least 20 ules from pinpoint to bean size. These began ut 50 centimeters from the ileocecal valve and tinued proximally for about 200 centimeters. of these nodules had eroded through the serosa ch caused a kinking of the intestine. Approxiely 170 centimeters of ileum were resected and de-to-side anastomosis was made. It was beed by the surgeon that intestine involved with cinoid was left. The postoperative course was plicated by a lung abscess which required drain-. X-ray studies of the intestine postoperatively ed to show evidence of remaining tumor.

Microsection disclosed cords and masses of cells ch had penetrated to the serosa. The cells were form in size and shape with rare mitotic figures. s patient was asymptomatic in March 1952.

CASE 7. No. 318,957. A fourth case of ileal carcid was discovered incidentally during autopsy of 2 year old white male. He had no gastrointestinal mptoms and death was the result of cardiac failure. ring routine examination of the intestine, 3 subcosal nodules 0.3 to 0.5 centimeter in size, were covered about 25 centimeters apart along the disileum.

On microsection there was no evidence of invaon. The cells were small, uniform in size, and itoses were noted.

In 2 of these patients solitary tumors were found and in 2 the neoplasms were multiple; as many as 68 separate nodules have been reported in a single case. In 3 of our cases carcinoid cells had invaded the muscularis. In 2 of these, carcinoid tumors had invaded through the serosa of the intestine and incipient obstruction was present. One ileal carcinoid, found at autopsy, showed no evidence of invasion. In no case was there evidence of distant metastases. Microsection of

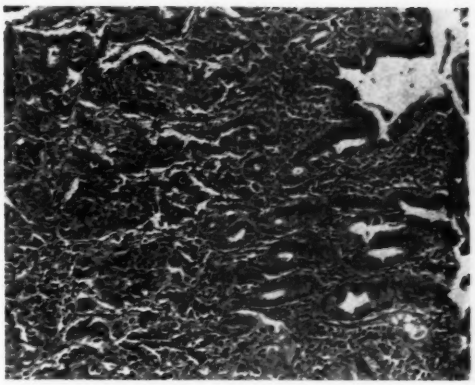

Fig. 2. Cords and masses of carcinoid cells growing from abnormal glandular elements of the duodenal mucosa.

all 4 lesions demonstrated cells, uniform in size and shape, and a rarity of mitotic figures. Two patients who were followed for 12 and 10 years respectively remained asymptomatic. A third patient was well 6 months postoperatively. In 1 patient, an asymptomatic carcinoid tumor of the ileum was associated with a carcinoma of the rectum and a basal cell cancer in the preauricular region.

Ileal carcinoids most often fail to cause symptoms until they invade the serosa and cause constriction, kinking, and various degrees of obstruction. Cooke found that the tumors were usually nodular and only 5 in a

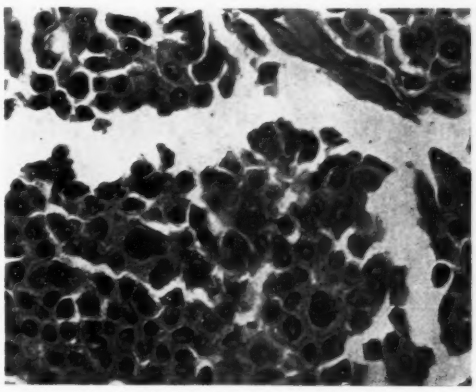

Fig. 3. Masses of disoriented carcinoid cells with very little supporting stroma. Large hyperchromatic multilobulated or multiple nuclei are frequent. Cytoplasm is granular. All borders are definite.

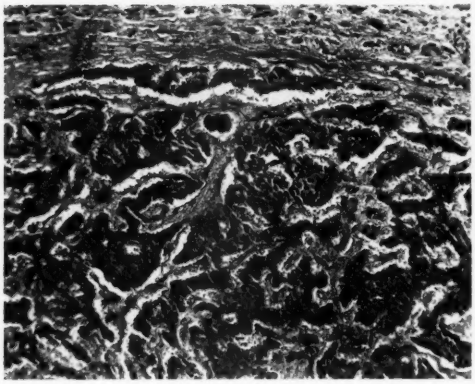

Fig. 4. Carcinoid cells in cords and strands metastatic in the liver.

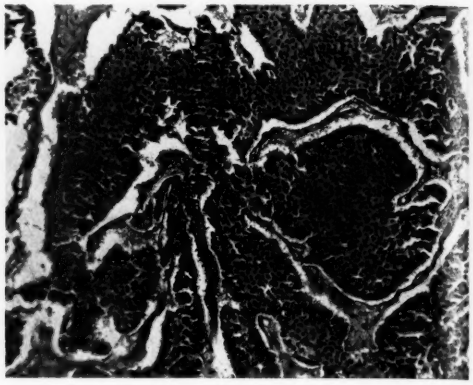

Fig. 5. Broad cords and masses of carcinoid cells in a celiac node. Note the small amount of supporting stroma.

series of 84 were annular. Grimes and Bell described a tetrad of recurrent obstruction, pain, diarrhea without blood, and weight loss, which they observed in 8 cases. They advised wide resection of the tumor and mesentery as the logical treatment. However, even with a small primary carcinoid, extensive metastases may be present. In such instances, only an enteroanastomosis can be done. Terplan, Weintraub and Wolf reported a case in which ileosigmoidostomy yielded palliation for 5 years. At autopsy following accidental death, no increase in size or extent of metastases was noted.

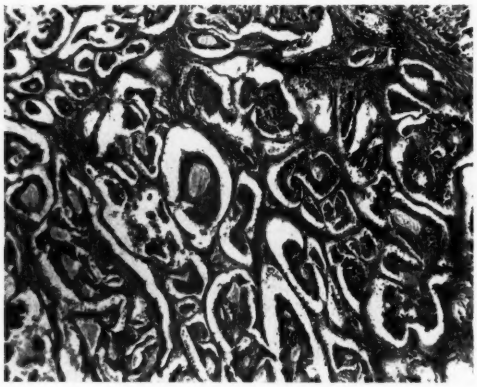

Fig. 6. Carcinoid cells in glandular acini containing "secretion" from an area continuous with region shown in Figure 4.

Two carcinoids were found in Meckel's diverticula.

CASE 8. No. 70,564. This 37 year old white male had an appendectomy in July 1936. The appendix was normal but a Meckel's diverticulum was present and was excised. The hospital course was uneventful.

Microsection presented a carcinoid with clusters of uniform cells and rare mitotic figures. The mucosa was not ulcerated nor was the serosa invaded. He expired in February 1950 from hypertensive disease. Autopsy was not obtained but during the intervening 14 years he had had no gastrointestinal symptoms.

CASE 9. No. 326,067. This 54 year old white male expired during August 1952, of Laennec's cirrhosis. An incidental autopsy finding was a Meckel's diverticulum which contained a nodule 0.3 centimeter in diameter near its tip. This was a carcinoid, well encapsulated, with no evidence of invasion. The cells were small, uniform in size, and mitotic figures were not seen.

Eight cases of carcinoid tumors in Meckel's diverticula have been reported most of which have been found at autopsy. None of these metastasized although Pautler and Scotti report infiltration into the muscularis in 1 case. Excision of the diverticulum is indicated. One case so treated remained free of symptoms for 14 years.

Three cases of cecal carcinoid were found:

CASE 10. No. 148,042. This 30 year old white male was admitted in November 1944, bleeding grossly from the rectum. During June 1944, an ileotransverse colostomy was done to by-pass a neoplasm filling the right lower quadrant. Microscopic

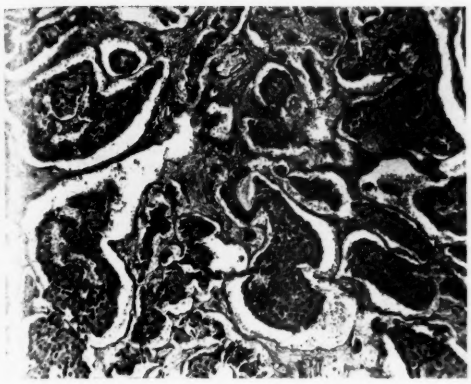

Fig. 7. Carcinoid cells in thick cords and masses with glandular element showing a cell mass growing from its wall.

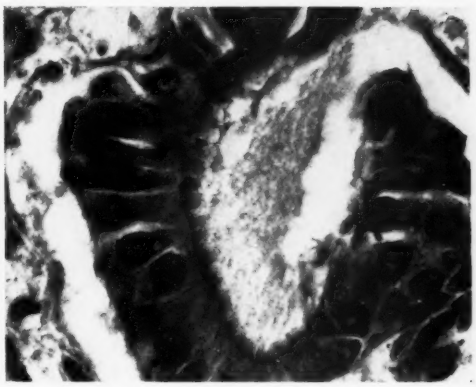

Fig. 8. Higher magnification of the glandular element in Figure 6, showing columnar cells with a distinct cuticular border.

diagnosis of the tissue removed was carcinoid of the cecum. Postoperatively improvement was noted and weight gained but soon an increase in the size of the mass was noticed. By October 1944, rectal hemorrhages recurred. Examination confirmed the increase in size of the mass, presence of anemia, and gross blood in the rectum. Liver demonstrated a functioning ileocolostomy but no visualization of the cecum and ascending colon. X-ray therapy, 5,500 roentgens through 3 portals, was administered to the right lower quadrant with insignificant improvement. During July 1945, a second large mass appeared in the epigastrium and a third in his right flank. Large nodes were present in the right groin. Constant severe abdominal pain and gross rectal bleeding were evident. Further x-ray radiation was given without effect and he expired in August 1945, 14 months after the initial surgery.

Microsection demonstrated an ulcerated surface with tumor cells exposed upon the surface. The tumor was in poorly defined cords and masses with no glandular formation (Fig. 10). Multiple, scattered areas showed large masses of disoriented cells which had little supporting stroma. Mitoses were present in numbers exceeded in only 1 other case in this series. The nuclei were large, hyperchromatic, and distorted (Fig. 11). Nucleoli were noted frequently. Veins and lymphatic channels were invaded. The histologic picture was unmistakably of malignancy.

CASE 11. No. 250,723. This 60 year old white male was admitted in November 1949, with mid-abdominal colicky pain, melena, and constipation of 4 weeks' duration. Systolic murmurs were present in the aortic and mitral areas and a roentgenogram of the chest visualized an enlarged heart and aortic calcification. The liver was palpable 2 fingerbreadths below the costal margin, and a round, tender mass was present in the cecal region. Barium enema failed to reveal a lesion but obstructed the bowel. Abdominal exploration revealed a tumor mass involving the cecum near the ileocecal valve. Metastases to the mesentery of the small intestine, the right and left lumbar gutters, gallbladder, liver, cul-de-sac, and peritoneum were present. An ileotransverse colostomy was done. The postoperative course in the hospital was uneventful but he expired at home, 1 month later.

Microsection showed carcinoid cells arranged in cords, nests, and strands. Many cells had large vesicular nuclei with a definite nuclear membrane and cytoplasmic granules which were eosinophilic. The large nuclei had a fine reticulated chromatin and

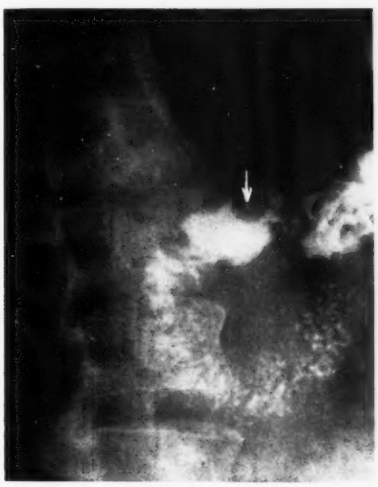

Fig. 9. Roentgenogram revealing a filling defect in the duodenum.

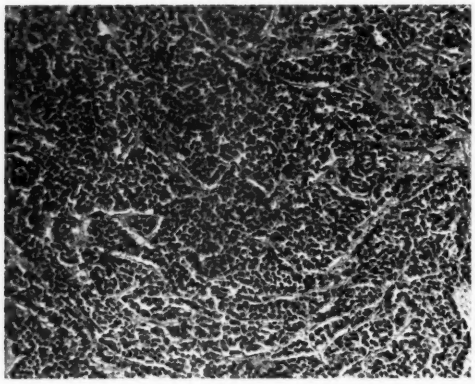

Fig. 10. Carcinoid cells arranged in poorly defined cords and masses with scanty supporting stroma. Loss of polarity is present.

mitoses were numerous. Cells were present in venous and lymphatic channels. The neoplasm appeared malignant.

CASE 12. No. 111,349. This 71 year old white male was admitted for an elective cholecystectomy, complaining of right upper quadrant colicky pain and tenderness, and weight loss of 60 pounds during the past 5 months. Recent weight loss was evident and para-umbilical tenderness was present over a questionable mass in that area. Feces were positive for occult blood but blood counts were within normal limits. X-ray films visualized a calculus in the fundus of the gallbladder and a deformity in the colon. A cholecystectomy was done. At surgery the cecum and the lower portion of the ascending colon were firm and rubbery in consistency and grayish-white in color. The appendix appeared to be involved by the same process. There were multiple nodes in the mesentery of the ascending colon. A biopsy and ileotransverse colostomy was done. The hospital course was uneventful.

Microsection of a lymph node showed cords of carcinoid cells which appeared well differentiated. The nuclei were rounded and uniform. Follow-up of this patient could not be obtained.

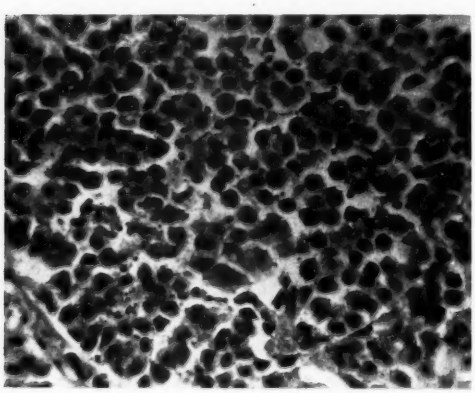

Fig. 11. Higher magnification of an area from Figure 8 shows anaplastic, disorientated cells with very little supporting stroma. Irregular, multilobulated, and multinucleated hyperchromatic nuclei are numerous.

All 3 of the cecal carcinoids had metastasized. The average survival in the patients followed was only 8 months, the average age 54 years. One patient received x-ray irradiation without benefit. In all 3 patients an ileocolostomy was performed with symptomatic relief. These tumors metastasized widely. Deposits were noted in the mesentery, peritoneum, gallbladder, cul-de-sac, liver, and inguinal nodes. Horn reviewed 15 cases of cecal carcinoids. Five cases were indistinguishable from adenocarcinoma by history, physical examination, laboratory study, or by gross examination at surgery. However, 1 patient, a 69 year old woman, was free of metastases and survived a right colon resection for 7 years and 11 months even though the cells showed marked pleomorphism and many mitotic figures. In 1 case reported by Brown metastasis had developed, while Altman presented the case of 1 patient with a huge primary tumor and widespread metastases who expired after an ileotransverse colostomy. Including the 3 cases in our series, 20 cecal carcinoids have been reported and 13 of these have shown metastases. In our study the tumors, microscopically and clinically, appeared malignant, and little, if any, benefit was derived from ileotransverse colostomy or x-radiation therapy. Thus the operation of choice is a right hemicolectomy.

Nine rectal carcinoids (plus 1 doubtful case, Case 22) were found:

CASE 13. No. 300,969. This 58 year old white male was admitted to the hospital complaining of ulcer-like abdominal pain, 8 pound weight loss, and anorexia of 6 months' duration. He had no rectal complaints, but on routine rectal examination a smooth, spherical tumor 6 centimeters from the pectinate line on the left lateral surface of the rectum was found. The mass was fixed at its base and infiltrated laterally. Proctoscopy revealed a submucosal mass, grayish-yellow in color, which was not ulcerated or bleeding, and which on biopsy was

Fig. 12. Carcinoid of rectum removed by abdominoperineal resection. The second primary is shown.

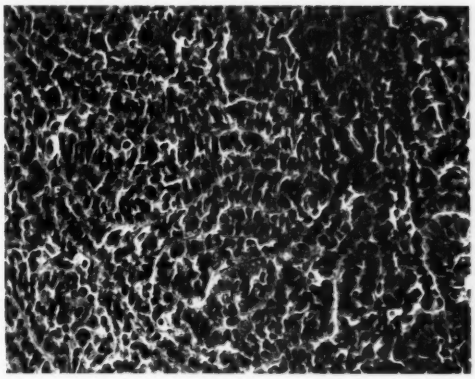

Fig. 13. Carcinoid cells arranged in poorly defined cords with little supporting stroma. Mitoses are frequent.

shown to be a carcinoid. A barium enema demonstrated a filling defect in the rectal ampulla but no other defect. A roentgenogram of the chest was normal. A diagnosis of duodenal ulcer was verified by a roentgenogram, and he responded well to medical treatment. All other laboratory studies were within normal limits. The patient was discussed widely by medical and surgical consultants and it was the consensus that radical excision be performed. A Miles abdominoperineal resection was done. The liver was found to contain multiple whitish-yellow nodules ranging from 1 to 3 centimeters in size. The nodes along the aorta and inferior mesenteric arteries were not enlarged. His hospital course was uneventful, his wounds healed well, and he was discharged in October 1951. Fifteen months later he was in good general health.

The gross specimen consisted of the sigmoid colon, mesentery, and rectum (Fig. 12). A spherical mass, 6 centimeters in diameter and covered with attenuated mucosa, was localized 8 centimeters from the pectinate line. A second tumor 1 centimeter in size was present 5 centimeters from the pectinate line. No other masses or enlarged nodes were found. On cut surface the tumors appeared well encapsulated, grayish-yellow in color, and uniform in consistency. Microsection of the rectal biopsy showed the surface partially denuded and the glandular elements almost entirely replaced by tumor cells growing in cords and diffuse masses with complete loss of orientation. The nuclei were large and vesicular with fine chromatin strands and one or more prominent eosinophilic nuclei. Microsection of the surgical specimen was similar to that noted in the biopsy. The cells were arranged in thick and thin palisading and reticulated cords in some areas and larger sheets and disoriented masses in others. There was evidence of old, as well as recent, hemorrhage into the tumor tissues. Mitotic figures were moderately frequent. Glandular elements were absent, although pseudoglandular formations were present. Definite invasion of lymphatic and vascular channels was encountered and the specimen showed features characteristic of malignancy.

CASE 14. No. 158,643. This 58 year old white male was admitted complaining of bright red rectal bleeding of 8 months' duration. No change in bowel habits nor weight loss was noted. Physical examination was normal except for rectal examination which disclosed an anorectal growth 2 centimeters from the anal canal in the anterior median line and 4 centimeters in diameter. A second sessile growth 0.5 centimeter in size was present on the posterior wall of the rectum. The bowel was otherwise normal for 24 centimeters from the anus. Laboratory tests and x-ray films were within normal limits. Biopsy of the larger lesion and excision biopsy of the smaller one were reported as carcinoid. In January 1944, a tumor 4 by 3 by 2 centimeters was excised by sharp

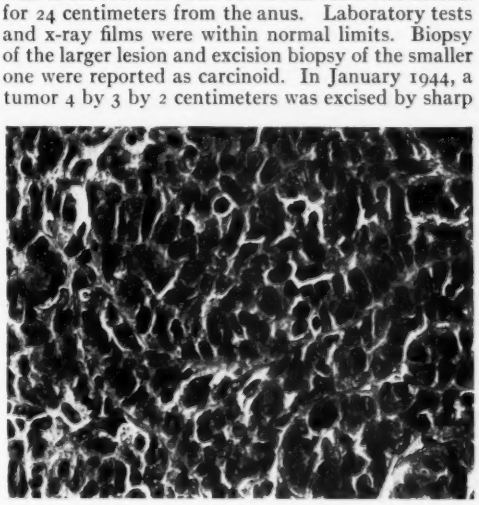

Fig. 14. Higher magnification of an area of Figure 10 shows large misshapen vesicular nuclei and several mitoses.

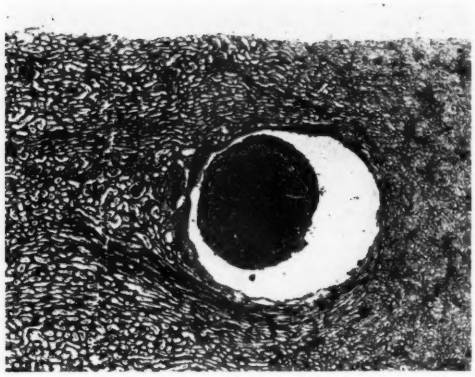

Fig. 15. A mass of carcinoid tumor cells which has entered a vein in the kidney by retrograde growth from the vena cava.

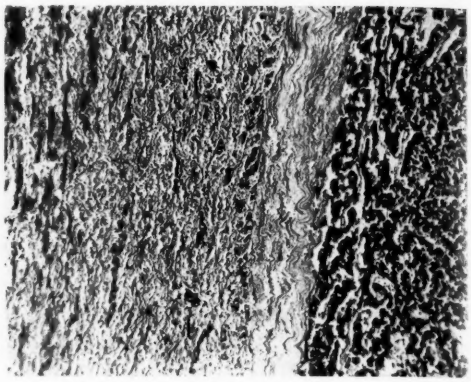

Fig. 16. The vena cava filled with carcinoid tumor arranged in folded and interconnecting cords. The wall of the vena cava is present.

dissection under spinal anesthesia. It was felt that the mass was excised completely without transecting the tumor, and the surgical wound was closed primarily. The postoperative course was uneventful. He was rehospitalized, 22 months postoperatively, again complaining of rectal bleeding. Examination disclosed a hard growth at the anal margin 2 by 2.5 centimeters in size. Inguinal nodes were enlarged bilaterally and the liver was palpable. Biopsies of the rectal lesion and the inguinal nodes were reported as carcinoids. A roentgenogram of the chest was normal. He was discharged without further treatment. By January 1946, rectal bleeding, severe right abdominal pain, and an abdominal mass were present. He expired February 1947, with clinical evidence of hepatic and pulmonary metastases, 46 months after the onset of symptoms. No autopsy was obtained.

Microsection of the surgical specimen showed a solid mass of tumor cells arranged in poorly defined cords with little supporting stroma (Fig. 13). Mitotic figures were very numerous (Fig. 14). Many nuclei were large, vesicular, with fine reticulated chromatin, and definite nucleoli. Microsection of the recurrent rectal lesion showed a structure similar to that of the primary. Carcinoid cells had penetrated the perirectal fat and were present inside vascular channels. The central parts of some of the tumor masses were necrotic.

CASE 15. No. 190,838. This 56 year old white male entered the hospital complaining of occasional bright red rectal bleeding. Physical examination was normal except for rectal examination which revealed a papillomatous growth 1.0 centimeter in width and 2 centimeters in length on the anterior rectal wall 6 centimeters from the anus, with no evi-

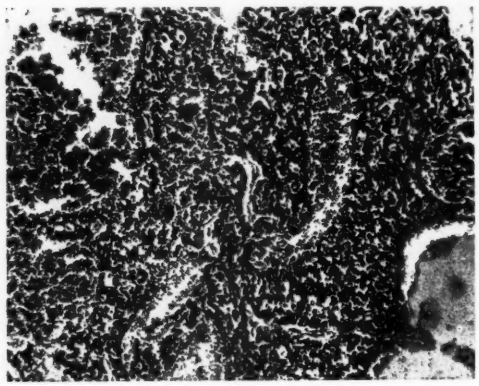

Fig. 17. Carcinoid tumor in cords and broad bands interlaced with large irregular blood filled spaces.

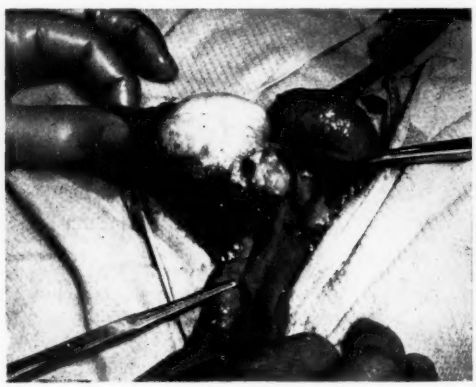

Fig. 18. Appendix containing both mucocele and carcinoid.

dence of induration surrounding its base. Proctoscopy was otherwise normal to 25 centimeters. Rectal examination had been reported as negative at a previous examination 7 months previously. Biopsy was reported as carcinoid. A chest roentgenogram and barium enema were normal. In July 1947, local excision of the tumor with a cuff of normal mucosa was accomplished under spinal anesthesia. The postoperative course was uneventful and the surgical specimen diagnosed as circumscribed carcinoid. The carcinoid cells were uniform in size and mitotic figures were rare. The mucosa was not ulcerated and the muscularis was not invaded. When last contacted in March 1952, almost 5 years postoperatively, he was asymptomatic.

CASE 16. No. 288,165. This 40 year old white male was admitted for repair of an inguinal hernia. On routine proctoscopic examination, a solitary pale polyp 0.4 centimeter in diameter was noted on the right lateral rectal wall 11 centimeters from the anus. There was no ulceration. Excision biopsy was performed and after return of the biopsy report as carcinoid, he was reproctoscoped and the site of the tumor fulgurated. Microscopically the mucosa was intact but the glandular structures were distorted by cords of carcinoid cells which penetrated into the muscularis. There was only slight variation in the size of the cells and few mitotic figures were noted. In May 1952, 17 months postoperatively, he was asymptomatic.

CASE 17. No. 285,058. This 57 year old white male entered the hospital complaining of a watery diarrhea of 6 to 8 stools per day of 4 months' duration. There was no pain or loss of blood but he had a recent weight loss of 12 pounds. A course of emetine and diodoquin before admission had failed to relieve him. Physical examination, stool studies, except 1 which was positive for blood, and rectal examination were negative. At proctoscopy small pedunculated polyps were visualized at 13 and 15 centimeters, and a sessile polyp 0.3 centimeter in size was seen at 10 centimeters on the anterior wall. The sessile polyp was diagnosed as a carcinoid after excision biopsy. The base of the carcinoid then was fulgurated proctoscopically. His diarrhea improved on medical management, and he was discharged as improved in March 1951. In May 1952, 15 months postoperatively, he complained of rectal pain but his general condition was good and he was gaining weight.

Microscopically, masses and cords of uniform carcinoid cells with small, darkly staining nuclei were noted. Tumor cell cords had penetrated into the muscularis. The mucosa was intact.

CASE 18. No. 296,680. This 55 year old negro male was hospitalized in May 1951, for bleeding duodenal ulcer, which responded well to medical management. On routine proctoscopy a 0.4 centimeter sessile polyp on the anterior wall of the rectum 7 centimeters from the anus was noted and an excision biopsy obtained. A pedunculated polyp 1 centimeter in size at the anal margin also was present and was biopsied. Biopsy of the sessile polyp revealed carcinoid while the pedunculated polyp was a papilloma. The carcinoid cells showed no evidence of invasion and the mucosa was intact. The cells showed no evidence of malignancy.

CASE 19. No. 309,405. This 38 year old negro male was admitted complaining of cramping abdominal pain and vomiting of short duration which quickly subsided without therapy. On digital rectal examination a 0.3 centimeter nodule was felt overlying the prostate gland. An excision biopsy showed it to be a carcinoid. He left the hospital after biopsy and failed to return for fulguration.

CASE 20. No. 185,003. On admission this 28 year old white male complained of rectal bleeding of bright red blood after bowel movements for 1 year. On digital rectal examination a 0.5 centimeter nodule 6 centimeters from the anal margin was found and excised during a hemorrhoidectomy in March 1947.

Microscopic examination disclosed a carcinoid with palisade type of growth, uniform small cells, and no mitotic figures. His postoperative course was uneventful.

CASE 21. No. 129,067. This 49 year old white male entered Hines Veterans Administration Hospital, in January 1943, for treatment of mild diabetes. He had no rectal complaints but on rectal examination a firm, 1.5 centimeter nodule 6 centimeters from the anus on the right anterolateral wall was felt. It was surrounded by a 1 centimeter zone of induration. Barium enema and proctoscopy were otherwise negative. The tumor was excised widely including a 2 centimeter mucosal cuff and the defect was closed primarily.

Microsection revealed a well circumscribed carcinoid without mitoses. He was well and without recurrence 9 years later.

CASE 22. No. 233,453. This 40 year old white male had had pain in the coccygeal region since 1945. In July 1948, a presacral tumor was removed and diagnosed as "neurocytoma, possible carcinoid." In April 1949, a transurethral resection became necessary because of dysuria, secondary to increasing growth of the tumor. In July, 1951, cordotomy was necessary. He was given x-ray therapy to the area without improvement. He expired in June 1952 and a limited autopsy was permitted. Five hundred cubic centimeters of ascitic fluid were present. Five or 6 yellowish-white and hemorrhagic nodules were present in the liver. Masses of tumor were present along the diaphragm, in the pelvis, and around the aorta; the adrenal glands could not be found. The right kidney was invaded (Fig. 15), and the inferior vena cava was completely blocked by tumor. There was a tumor on the posterior of the true pelvis which was adherent to the rectum. Specimens from all these areas were interpreted as carcinoid. It was impossible in this limited autopsy to be certain of the primary site although it appeared to be the rectum. (Epps, White, and Hanan have reported a case of rectal carcinoid first manifested by a metastasis in the broad ligament.)

Microsection of the original presacral mass showed large masses of uniform cells arranged in cords and masses and gland formation. The nuclei were round and vesicular with a reddish, slightly granular cytoplasm. Many mitotic figures were present. Lymphatic and venous channels were invaded by masses of tumor cells. Sections of tumor in the liver, adrenals, kidneys, vena cava, cul-de-sac, and other areas all showed tumors similar to the original biopsy. The vena cava and other large vessels were completely occluded by masses of tumor (Fig. 16). Many large tumor masses which grossly appeared like a bloody sponge had large spaces filled with blood within them (Fig. 17). Individual cells were rather uniform in size. Mitotic figures, however, were quite numerous in some specimens, and invasion through the tissue and vascular channels was a very marked feature in this case.

Nine rectal carcinoids were studied. Two of these measured 5 and 4 centimeters in largest diameter and were malignant as manifested by metastases. Seven of these were less than 1.5 centimeters in diameter and were benign in clinical course. One carcinoid in a 58 year old man recurred in 22 months after local excision and caused death in 37 months with inguinal, hepatic, and pulmonary metastases. Another in a 56 year old man although completely asymptomatic when 5 centimeters in diameter had disseminated to the liver. The 7 clinically benign tumors were detected at an average age of 46 years, and in 4 instances on routine proctoscopy or rectal examination. Three patients had rectal symptoms for which proctoscopy was done. In 5 instances the carcinoid was described as a pale sessile nodule 3 to 6 millimeters in diameter; in 2 a polypoid growth was found. In 2 cases digital rectal examination 18 and 32 months previously had been recorded as negative. Seven of the tumors were anterior and 2 were lateral in position. None were reported as posterior. In 2 cases 2 simultaneous carcinoids were present in the rectum; both were malignant. Rigdon and Fletcher reported the case of 1 patient with innumerable rectal nodules but with no distant metastases. Mayo and McKee found 3 multiple primary tumors, only 1 of which had metastasized, in a group of 66 cases which they reviewed. Recent cases have been reported by Tavenner, Freund, Cohen, Epps, Rosser, and Foreman. Our 9 proved cases bring the total to 103 of which 14 or 13.5 per cent have been malignant.

Malignancy seemed to be correlated with size in our series; the 2 tumors larger than 2 centimeters in diameter exhibited metastases. We concur with the recommendations of Mayo, Hines, and Shepard who advocate local excision in rectal carcinoids which are less than 1 or 2 centimeters in diameter if there is no evidence of extension. Lesions which are greater than 2 centimeters in diameter or which show evidence of infiltration, ulceration, or are annular or multiple should be excised radically. At this hospital the Miles operation is preferred. A combined abdominosacrococcygeal approach with pull-through and direct primary anastomosis could be feasible in a limited number of lesions properly situated. Local recurrence was noted in less radical excisions by us and Tavenner.

We believe that all rectal carcinoids, regardless of size, have a malignant potential and concur with the statement of Raven that "the formation of metastases is only a matter of time, although the degree of malignancy is less than in adenocarcinoma. As the tumor enlarges the cells will eventually transgress their barriers." Gersach in discussing the paper by Freund described a 1 centimeter rectal carcinoid which, untreated, increased to 2.5 centimeters in size in 5 years and caused death from metastases. The rectal carcinoids which were still small and localized in our series were found at an average age of 46 years while those which had metastasized were found at an average age of 57.

The value of routine rectal examination is re-emphasized; 4 tumors were incidental discoveries in our series. However, Hines reported only 3 carcinoids in 30,000 proctoscopies and Jackman an incidence of 4.6 per cent in a group of 87 rectal nodules.

Five appendiceal carcinoids were found.

CASE 23. No. 244,015. This 50 year old white male entered the hospital complaining of epigastric distress which was interpreted as due to duodenal ulcer and which responded to medical treatment. However, a mass was palpated in the right lower quadrant and barium enema revealed a filling defect in the cecum. Exploratory laparotomy in August 1948 revealed an appendix with a mucocele and a carcinoid (Fig. 18), and an appendectomy was performed. When last heard from he had no further distress in the right lower quadrant.

Microscopic examination revealed cords and nests of cells which had penetrated the full thickness of the appendiceal wall. The cells were uniform in size and no mitoses were seen.

CASE 24. No. 232,251. This 36 year old white male was admitted with symptoms and findings of acute appendicitis. Several previous episodes were acknowledged. Appendectomy revealed the appendix to be 8 by 1 centimeter in size, white, and fibrotic. In the submucosa on microscopic examination, nests of carcinoid cells infiltrating the muscularis were noted.

CASE 25. No. 185,161. This 34 year old white male was admitted with cholelithiasis, proved by roentgenogram. Cholecystectomy was performed and the appendix removed incidentally.

Microscopically, a carcinoid was found at the tip of the appendix. The cells were large and uniform in size and no mitoses were seen. The cells infiltrated through muscularis to serosa. In May 1952, 5 years postoperatively, he was asymptomatic.

CASE 26. No. 135,546. This 54 year old white male was admitted in 1940 with large bowel obstruction, secondary to carcinoma of the sigmoid. Primary colostomy was done. Later a Mikulicz type of resection on the sigmoid lesion was done and an incidental appendectomy was performed. The tip of the appendix was bulbous, yellow, and 2 centimeters in diameter.

Microscopic examination revealed a carcinoid infiltrating the muscularis. He expired in February 1944; no autopsy was obtained.

CASE 27. No. 325,640. This 41 year old white male underwent appendectomy in July 1952.

Microscopic section revealed a carcinoid which had penetrated to the serosa and invaded lymph vessels as well as periappendicitis. The cells were uniform in size, and no mitoses were seen. The postoperative course was uneventful.

In 2 of these cases the tumors were found at appendectomy for acute appendicitis while in 3 they were incidental findings. All 5 patients have shown clinically benign courses, although in all, carcinoid cells infiltrated the muscularis of the appendix and, in 1 instance, the lymph vessels. Lemmer found 2 of 26 appendiceal carcinoids to be malignant while D'Ingianni found that 3 of 29 had metastasized to lymph nodes and 10 had penetrated through the muscularis to the serosa. It appears that carcinoids of the appendix are as potentially capable of metastases as carcinoids in other locations. Early symptoms usually lead to appendectomy and removal of the lesion before spread had occurred. Because in 1 case we found invasion of the lymphatics we believe that wide resection of the mesoappendix should be done.

PATHOLOGY

Carcinoid tumors wherever found have a similar gross and microscopic appearance. They can be demonstrated to arise from cells of the glands of Lieberkühn and may assume a variety of histologic patterns all of which may appear in the same tumor. The most frequent pattern is one of cords, strands, and solid nests of cells. At times there is a palisade-type of growth of distinctly columnar cells which may show a definite orientation. The palisaded strands may interconnect to form a reticular pattern. Frequently the cell cords form pseudoglandular structures and at times definite glandular acinar formations are numerous even in distant metastases. These are formed of columnar cells which may or may not have a cuticular border similar to cells of the intestine. Often a reddish stained secretion occupies the lumen. From the cells of the acinar walls solid masses and cords grow in a manner similar to the origin from the crypts of Lieberkühn. Almost always there remains some indication of the basic glandular pattern of growth. The lumen often is minute and bounded by cells more undifferentiated than columnar cells and resembling the more typical carcinoid cell.

The carcinoid cells typically show a cytoplasm containing numerous eosinophilic granules which can be impregnated with silver. The grossly yellow tumors show cells with well developed granularity while in white or gray tumors the granularity is not prominent. The color of the tumor ranges from grayish-white to yellow and reflects the content of lipoids such as cholesterol and lecithin.

The tendency of carcinoid tumors to enter lymphatic channels early and expand them by their growth but to metastasize slowly to regional nodes is characteristic. The smallest tumor we examined, almost undetectable grossly, and benign in cellular characteristics, had already penetrated the muscularis of the appendix and filled several lymph channels. Many other small carcinoids penetrated the muscularis, yet only 1 less than 0.5 centimeter in diameter showed a malignant cellular pattern and had metastasized. A small primary carcinoid may, nevertheless, be a source of widespread metastases. In general although

small tumors tend to be benign and large ones malignant with distant metastases, every carcinoid must be regarded as a neoplasm of potential malignancy.

Malignancy histologically, we believe, is determined by the usual features applied to other types of carcinoma, namely, cellular size, pleomorphism, frequent mitoses, and invasiveness. Raiford and Pearson and Fitzgerald believed there was no correlation between microscopic appearance and clinical course, but in our series the tumors exhibiting frequent mitoses and pleomorphism were rapid in growth and spread. Others have reported metastases which remained unchanged in size for years. Although in some cases malignancy is immediately apparent while others at first appear benign we believe, as does Bailey, that extension into the muscularis and to the serosa is a definite indication of malignancy even though individual cells may be uniform and well differentiated. The tumors usually lack a definite capsule.

Metastases in our series were not found above the diaphragm except for 1 unproved exception. The usual pattern is involvement of the regional lymph nodes followed by liver metastases via the portal system. However, when the tumor becomes large, the primary lesion or metastases may seed the peritoneum extensively. The systemic vascular tree may be invaded and tumor cells may fill the larger venous channels. Perineural invasion may also occur. Metastases have been reported in the lungs, liver, spleen, adrenals, kidneys, subcutaneous tissue, bone marrow, and in the brain.

The tumors of our series were nodular or pedicled. Annular growths have been reported but may in part represent fibrous and muscular reaction to the carcinoid. Multiple carcinoids were present in 4 of our cases and all appeared to be multiple primary tumors rather than metastases. In 2 of these 4 cases, both rectal, distant metastases were present. Three of our carcinoids were associated with other carcinomas of the large bowel or rectum. In 1 patient a carcinoid of the ileum, carcinoma of the rectum, and basal cell carcinoma of the skin all existed simultaneously. Cruickshank and Cunningham believed that "carcinoid is no more unusual than any other tumor in a multiple tumor complex."

Carcinoids tend to become fatal more slowly than other gastrointestinal carcinomas. None of our patients in whom the growth was still localized have died from carcinoid or developed recurrences after adequate surgery. We have patients living without evidence of recurrence 9, 10, 12, and 14 years postoperatively. In 8 cases there was evidence of metastases; 6 of these patients have died of their carcinoid, an average of 27.5 months after the diagnosis was made; 1 is living with hepatic metastases 15 months after an abdominoperineal resection, and 1 was lost to follow-up.

We observed metastasizing carcinoids in the duodenum, cecum, and rectum, and they have been reported in the stomach, gallbladder, ileum, and appendix. Pautler and Scotti found that none of 7 carcinoids in Meckel's diverticula had metastasized although in 1 case muscle invasion was noted. We believe that all carcinoids are equally malignant.

TREATMENT

The treatment of choice of carcinoid tumors is adequate surgical excision based on the sound premise of removal of the primary tumor, an adjacent zone of normal tissue, and the primary lymph draining region. In the case of small tumors which are accessible to repeated follow-up examination, as in the rectum, local excision with fulguration probably is adequate. Should recurrence develop, radical surgery should be done. X-ray therapy was used in 2 cases without benefit. Brown treated the mesenteric metastases of an ileal carcinoid with 3,000 roentgens. When the tumor was removed 2 months later no gross or histologic effect of x-ray was seen.

CONCLUSIONS

A study of 27 cases of carcinoid warrants the conclusions that all carcinoid tumors of the gastrointestinal tract are potentially malignant. Variations in the percentage of metastases appear only to reflect earlier symptomatology. In 8 of our cases metastases had occurred and these were duodenal, cecal, and rectal in origin. No distinguishable microscopic features were revealed in carcinoids

from these various sites; all showed muscle infiltration, lymph vessel invasion locally, and pleomorphism. It appears that the degree of pleomorphism and mitoses correlates with clinical malignancy. The treatment of choice is adequate surgical excision.

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DEMONSTRATION OF AN ANTIDIURETIC SUBSTANCE IN THE URINE OF POSTOPERATIVE PATIENTS

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POSTOPERATIVE oliguria has been studied as part of the metabolic response to surgery. Many factors, including dehydration, sodium retention, and transient rena hypoxia, may play a part. The role of the antidiuretic hormone (ADH) in the production of this oliguria has been alluded to but not definitely shown. Verney demonstrated a characteristic pattern of inhibition of urinary flow in response to the antidiuretic hormone. Hayes has shown a similar pattern of inhibition of urinary flow following surgical anesthesia, and he considers this indirect evidence of the release of the antidiuretic hormone.

The purpose of this study was to determine whether there is excreted in the urine of hydrated patients in response to surgery an endogenous antidiuretic substance (ADS) which can be extracted and demonstrated by bio-assay. The presence or increase of such a substance in the postoperative urine of patients might then be considered suggestive evidence of the elaboration of the antidiuretic hormone of the posterior pituitary as a part of the neuroendocrine response to surgery and thus a factor in the production of postoperative oliguria.

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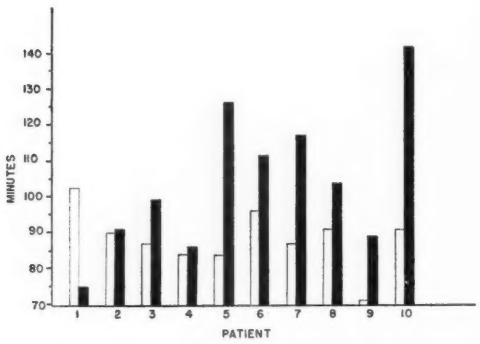

Chart 1. End points of rat excretion of standard load. □, Preoperative urine extracts. ■, Postoperative urine extracts.

METHODS

Clinical material. The subjects of this study were 10 patients undergoing major surgery on the general surgical service of University Hospitals of Cleveland. Seven patients were operated upon under general anesthesia; 3 had continuous spinal anesthetics (Table I). Two 24 hour urine specimens were obtained from each patient. The preoperative specimen contained all urine excreted during the 24 hours prior to the patient's departure from the division to surgery. The postoperative specimen contained all urine excreted during the following 24 hours, including the time spent in surgery. These patients received fluids during both the preoperative and postoperative periods in order to eliminate marked dehydration as a stimulus for the elaboration of an antidiuretic substance. None of the patients had any evidence of renal disease.

Extraction of the antidiuretic substance from the urine. The antidiuretic principle was extracted from the urine specimens by the method of Grollman and Woods. This involves quantitative adsorption on activated charcoal, elution from the latter by glacial acetic acid, and precipitation from the last named by petroleum ether and absolute alcohol. Our only modification of their method was the substitution of low speed centrifugation for filtration in the separation of urine from charcoal. Following precipitation, the antidiuretic principle was kept in the desiccated state until bio-assay in rats could be performed—always within 48 hours. Grollman states that in aqueous solution the active principle undergoes deterioration; in the solid dry form it should

be stable over a long period of time and in this manner avoid the necessity of its immediate assay.

Bio-assay. Bio-assay of aliquots of the extract was performed in rats, using Ralli's modification of the method of Burn in which adult male Sprague-Dawley rats in normal nutrition and hydration are further hydrated to 5 per cent of their weight by means of tap water gavage. This is followed immediately by intraperitoneal injection of 1 cubic centimeter of the urinary extract. The rats are then placed in metabolism cages and the urines collected and measured at 15 minute intervals. The end point was taken as the time when the volume of urine excreted was the equivalent of 50 per cent of the gavage solution. Eight rats were used for each assay, 4 controls receiving aliquots of the preoperative urine extracts, the other 4 receiving aliquots of the postoperative urine extracts.

RESULTS

The extracts of postoperative urine from 9 of 10 hydrated patients when injected into rats produced a delayed excretion of a standard gavage solution (Chart I). One of the 10 postoperative extracts produced a more rapid excretion when compared with its control.

The mean difference between the excretion end points of the rats which received extract from preoperative urines and those which received extract from postoperative urines was 15.6 minutes. (This figure has been analyzed for the significance of its difference from zero and the value of "t" is calculated as 2.24. $P = 0.05$.)

DISCUSSION

The identification of the substance extracted from urine in this experiment with the antidiuretic principle of the posterior pituitary has not been established. The extraction

TABLE I.—DATA ON PATIENTS AND RESULTS OF BIO-ASSAY

No.	Patient Age Sex	Operation	Anesthetic	Body wgt., kgm.	24 hr. preop. urine volume and sp. gr.	Postop. fluids, c.c.	24 hr. postop. urine volume and sp. gr.	Bio-assay of urine extract	
								Preop. minutes	Postop. minutes
1	R.F. 54 M	Resection of reduplication of esophagus	Na pentothal, endo.GOE, curare	51.8	1200 1.014	4500	400 1012	102	75
2	E.M. 46 F	Partial cholecystectomy, cholecystostomy	Cont. spinal (pontocaine)	114	1400 1.012	4800	1000 1010	90	91
3	H.L. 24 F	Total colectomy, ileoproctoscopy	Na pentothal, GOE, curare	45.3	1350 1.022	3200	1250 1016	87	99
4	C.B. 69 F	Abdominoperineal resection	I.V. seconal, cont. spinal (pontocaine)	60.5	1200 1.015	3000	800 1014	84	86
5	M.H. 45 F	Cholecystectomy	I.V. seconal, GOE	101	1700 1.017	3000	1250 1016	84	126
6	C.G. 36 F	Mitral commissurotomy	I.V. seconal, endo. GOE, curare	78.7	1700 1.005	3550	1400 1007	96	111
7	E.M. 32 F	Cholecystectomy, cholangiography	Endo. GOE	94.5	1100 1.014	2500	1000 1010	87	117
8	M.H. 52 F	Roux-Y cholecystojejunostomy	GOE	84	800 1.012	3000	400 1007	91	104
9	M.P. 34 F	Mitral commissurotomy	I.V. seconal, endo. GOE, curare	58	800 1.015	2850	320 1007	71	89
10	E.V. 69 F	Lysis of adhesions; resection of jejunum	Cont. spinal (pontocaine)	36	1800 1.007	2500	400 1014	91	142

method is based on the fact that ADH is adsorbed onto charcoal and it is not known whether other antidiuretic substances in the body are similarly adsorbed. Shorr has shown that ferritin (VDM), produced in the liver in both acute hepatic injury and in chronic liver disease, has an antidiuretic action, but he attributes this to stimulation of the posterior pituitary since its action does not take place in dogs with diabetes insipidus, the result of stalk resection.

The amounts of antidiuretic substance which we were able to demonstrate in the urine following surgery are not so large as those which have been shown by similar methods in cirrhosis with ascites, congestive failure with edema, eclampsia and preeclampsia, Cushing's syndrome, and in edematous patients with the nephrotic syndrome. In some of these, excretion delay periods of 300 to 800 minutes were found.

This suggests two possibilities: (1) The amounts elaborated *are* small. (2) Larger amounts than are recovered in the urine may be elaborated in response to the stress of surgery and are rapidly adsorbed and inactivated in the body before they can be excreted. Heller and Urban demonstrated a substance in human blood capable of rapid destruction of pituitrin. They showed in vitro adsorption of the ADH by blood and tissue suspensions with a specific adsorbing capacity of liver and kidney 58 and 8 times, respectively, that of blood.

Since several of the conditions in which an antidiuretic substance in urine has been demonstrated have concurrent liver disease or liver injury, less rapid destruction of the hormone may account for the finding of increased amounts of ADP in the urine. In view of the work of Heller and Urban it may be anticipated that larger amounts of the principle may be demonstrated in patients with liver disease who undergo surgery.

Further work in our laboratory will be undertaken to determine the effect of liver impairment, preoperative water loading, and dehydration on the excretion of ADS in the urine during the postoperative period.

SUMMARY

1. Extracts of a substance in postoperative urine from 9 of 10 hydrated patients, when injected intraperitoneally into normal rats, produced a significant delay in urinary excretion under standardized test conditions.

2. The identification of this antidiuretic substance with the antidiuretic hormone of the posterior pituitary has not been established.

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ACUTE OBSTRUCTION OF THE COLON

An Analysis of 205 Cases

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A RECENT review of 1,007 cases of acute mechanical intestinal obstruction occurring consecutively at the Charity Hospital in New Orleans during the 10 year period 1940 to 1949 indicated that the colon was the site of the obstruction in one-fifth of the cases. The mortality of small bowel obstruction was 15 per cent, a figure which compared favorably with that reported from most large general hospitals. A mortality of 32.7 per cent in the cases of acute colic obstruction was considered much too high. A detailed analysis of the 205 cases of large bowel obstruction was undertaken and forms the substance of this report.

MATERIAL

A series of 205 cases is reported, including all cases, with exceptions noted below, in which the diagnosis of acute large bowel obstruction was made on all services at the Charity Hospital over a period of 10 years (1940 to 1949, inclusive). Excluded from the study were all patients whose intestinal obstruction was due to paralytic ileus, malfunctioning colostomy, rectal stricture, congenital megacolon, impaction of feces, and neoplasm situated distal to the rectosigmoid. In addition, cases of colon cancer without signs and symptoms of obstruction indicating the need for prompt relief were not included. Only the cases of those patients are included who were proved by laparotomy or autopsy to have acute colon obstruction, or, if laparotomy or autopsy was not performed, who presented a clinical picture upon which a positive diagnosis could be established beyond reasonable doubt.

The age distribution by decades is presented in Chart 1. The youngest patient was 6 days old; the oldest 85 years. Patients over 60 years of age comprised 51.5 per cent of the material and 61.5 per cent of the deaths.

Fifty-five per cent of the patients were males; 45 per cent were females (Table I).

Negroes were afflicted somewhat more often than whites, the ratio being almost 5:4, while the ratio of negroes to whites in the Charity Hospital population during the period under study was about 3:2.

The anatomic distribution of the obstructing lesions is illustrated in Figure 1. In 70 per cent of the cases the obstructing lesion was situated at or distal to the splenic flexure, and the sigmoid was the site of the obstruction in 60 per cent.

At operation or autopsy 9.8 per cent of the patients were found to have strangulated obstruction. Unless the surgeon's note or the autopsy protocol specifically mentioned the presence of gross evidence of compromise of the circulation, or unless distention with ischemic necrosis had resulted in perforation of the bowel at some distance proximal to the site of the primary lesion, the case was classified as one of simple obstruction.

One hundred and sixty-three (82.7 per cent) of the patients had had symptoms of intestinal obstruction for more than 24 hours when admitted to the hospital, whereas only 17.2 per cent were early cases. In 8 cases the duration of symptoms was not recorded (Table I).

As in most reports, the common causes of obstruction were carcinoma and volvulus, accounting together for nearly three-fourths (73.6 per cent) of the entire series (Fig. 2). The incidence of carcinoma is relatively low (48.7 per cent) when compared with other reported series. Perhaps this is due to the fact that in the present survey were included only those cases of carcinoma which had produced a degree of obstruction requiring prompt relief. Twenty-five patients with complete ob-

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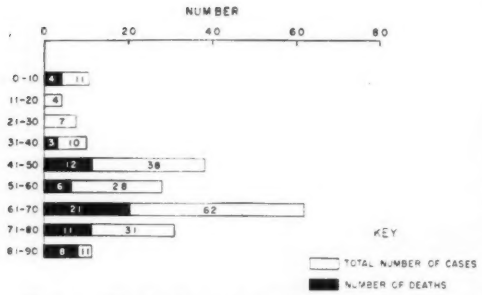

Chart 1. Distribution and mortality by age in 205 cases of acute colon obstruction. Patients over 60 years of age comprise 51 per cent of the material and 61 per cent of the deaths. The death rate of patients 60 years of age and younger is 25 per cent; above 60 years it is 38 per cent. The age is not recorded in 3 cases, 2 of which were fatal.

struction had incarcerated hernia sacs containing only large bowel. Colocolonic intussusception was the cause of obstruction in 12 patients, of whom 6 were adults. There were 5 cases of acute adhesive ileus, 5 cases of sigmoidal diverticulitis, 4 cases of abdominal carcinomatosis with extrinsic pressure producing sigmoidal obstruction, and 3 cases of complete obstruction due to extrinsic pressure by a pelvic abscess.

TREATMENT AND RESULTS

There were 67 deaths in the series of 205 cases, a mortality rate of 32.7 per cent. Seven patients were moribund on admission but are included in these totals.

The major factors influencing prognosis were the age of the patient and the site, type, duration, and etiology of the obstruction.

Patients over 60 years of age comprised 51.5 per cent of the material and 61.5 per cent of the deaths. The death rate up to and including 60 years of age was 25.5 per cent; above 60 years it was 38.6 per cent.

The mortality in relation to the site of the obstruction is shown in Chart 2. Patients with sigmoidal obstruction accounted for 60 per cent of the cases and 62 per cent of the deaths. The mortality rate in the 23 cases of transverse colon obstruction was 17.5 per cent, and in the cases of descending colon obstruction it was 57.1 per cent.

Twenty-nine per cent of the patients with simple obstruction died; while the mortality of strangulated obstruction was 65 per cent (Table I).

TABLE I.—ACUTE COLON OBSTRUCTION, MATERIAL AND RESULTS

	No. of cases	Per cent of cases	No. of deaths	Mortality, per cent
Total cases	205	100	67	32.7
Sex*				
Male	112	55.4	33	29.5
Female	90	44.5	32	35.5
Color†				
White	89	43.8	31	34.8
Negro	114	56.2	34	29.8
Type of obstruction				
Simple	185	90.2	54	29.2
Strangulated	20	9.8	13	65.0
Bowel resection				
Yes	21	10.2	13	61.9
No	184	89.8	54	29.3
Duration of symptoms‡				
Less than 24 hours	34	17.2	6	17.6
More than 24 hours	163	82.7	59	36.8
Site of obstruction				
Cecum	21	10.2	7	33.3
Ascending colon	7	3.4	2	28.6
Hepatic flexure	9	4.4	2	22.2
Transverse colon	23	11.2	4	17.5
Splenic flexure	14	6.8	5	35.7
Descending colon	7	3.4	4	57.1
Sigmoid	124	60.5	43	34.7
Etiology of obstruction				
Carcinoma	100	48.7	42	42.0
Volvulus	51	24.9	12	23.5
Hernia	25	12.2	4	16.0
Intussusception	12	5.8	4	33.3
Diverticulitis	5	2.4	0	0.0
Adhesions	5	2.4	1	20.0
Extrinsic pressure	7	3.4	4	57.1

*Not recorded in 3 cases.
†Not recorded in 2 cases.
‡Not recorded in 8 cases.

Resection was carried out in the presence of acute obstruction in 10.2 per cent of the cases, with a mortality rate of 61.9 per cent.

Of the patients seen within the first 24 hours of their illness, only 17.6 per cent died; the mortality was more than twice as high (36.8 per cent) in those who had been ill more than 24 hours.

The influence of etiology upon the mortality is demonstrated in Chart 3.

The Charity Hospital experiences with intussusception have been reported by Kahle and Becker, and will not be considered here.

In the present series of 205 cases of acute large bowel obstruction, volvulus and carcinoma together accounted for 73.6 per cent of the cases and 80 per cent of the deaths.

Acute volvulus of the sigmoid was encountered 45 times in 31 patients. There were 2 deaths among the 17 patients managed by proctosigmoidoscopic intubation. One patient died of myocardial infarction 48 hours after having been adequately decompressed, and in the other case decompression was adequate but an unrecognized gangrene later resulted in perforation and fatal peritonitis. Laparotomy and simple detorsion of the volvulus was done in 15 cases without a fatality. Resection with delayed anastomosis, usually employing the Mikulicz principle, was done in 8 cases with 4 deaths. Six of these patients had strangulated obstruction and were gravely ill. The 1 patient treated by primary sigmoidal resection with immediate end-to-end anastomosis survived. In 1 fatal case, an erroneous preoperative diagnosis of carcinoma of the sigmoid was made, and simple cecostomy was performed without exploration of the abdomen. A double closed-loop obstruction usually exists in the patient with acute volvulus of the sigmoid in the presence of a competent ileocecal valve, and proximal decompression alone is an illogical procedure.

The 3 patients with acute volvulus of the transverse colon were treated by operative reduction, with 2 deaths. One elderly patient died on the sixth postoperative day of ventricular fibrillation and cardiac decompensation. The other fatality occurred in a patient who was improperly treated by nonoperative tube decompression for 24 hours, and who died of shock 3 hours after operation.

There were 3 patients with acute cecal volvulus, 2 of whom survived. Simple operative reduction was done in one instance, and detorsion and cecostomy in another. In the fatal case, the gangrenous cecum and ascending colon were resected, and an ileotransverse colostomy and proximal tube ileostomy performed. Necropsy 3 days postoperation showed widespread bilateral bronchopneumonia.

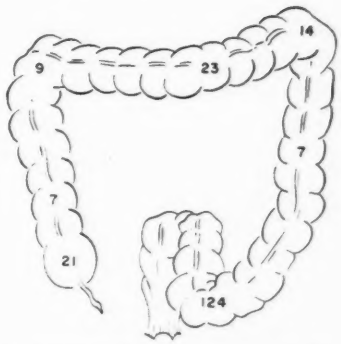

Fig. 1. Anatomic site of obstruction in 205 cases of acute obstruction of the colon.

Thus, including 2 patients who were moribund on admission, there were 12 deaths in the 51 cases of colon volvulus, a mortality rate of 23.5 per cent.

Michel has emphasized that the therapeutic method employed in the individual case of acute colon volvulus must vary with the site of the obstruction, the presence or absence of strangulation, and the general condition of the patient. Most patients with sigmoidal volvulus are best managed by emergency operative reduction, followed in a few days by elective resection with end-to-end anasto-

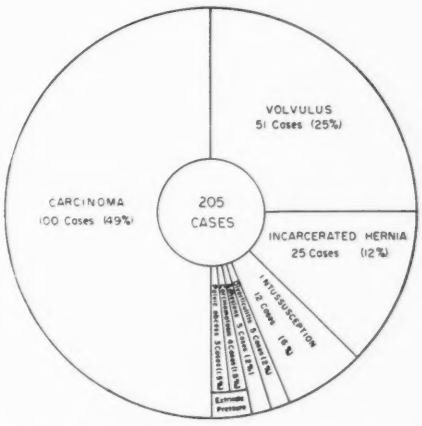

Fig. 2. Incidence of various etiologic types of colon obstruction occurring at Charity Hospital during the 10 year period 1940 to 1949. It is noteworthy that carcinoma was responsible for the obstruction in only one-half of the cases.

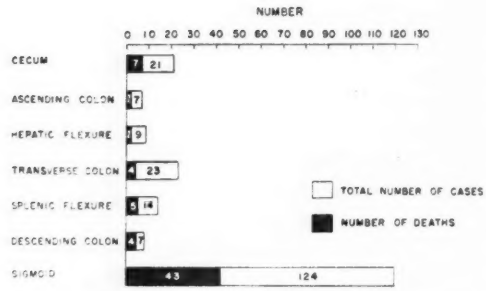

Chart 2. Distribution and mortality relative to anatomic site of obstruction. Patients with sigmoidal obstruction accounted for 60 per cent of the cases and 62 per cent of the deaths.

mosis. Emergency exteriorization resection is indicated in the presence of irreversible strangulation. Dean and Murray have reported a favorable experience with primary resection and immediate anastomosis in the treatment of early acute sigmoidal volvulus. Most surgeons believe that the danger to these patients is increased when attempts are made to combine the emergency and elective phases of treatment.

That recurrence of sigmoidal volvulus is sufficiently frequent to justify elective resection is demonstrated by the fact that of the 30 Charity Hospital patients who survived an acute attack, 9 (30 per cent) returned with at least one subsequent attack, and it was necessary for 4 (13.3 per cent) to return because of a fatal recurrence.

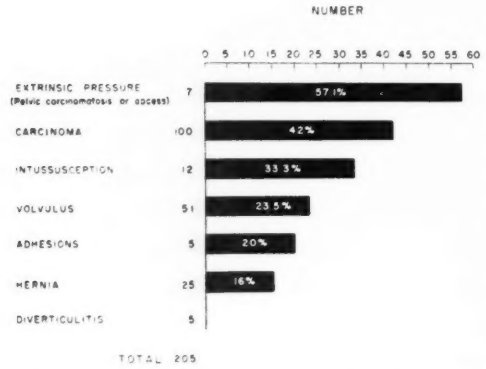
NUMBER
0 5 10 15 20 25 30 35 40 45 50 55 60
EXTRINSIC PRESSURE (Pelvic carcinomatosis or abscess) 7 57.1%
CARCINOMA 100 42%
INTUSSUSCEPTION 12 33.3%
VOLVULUS 51 23.5%
ADHESIONS 5 20%
HERNIA 25 16%
DIVERTICULITIS 5
TOTAL 205

Chart 3. The mortality in relation to etiology in 205 cases of acute colic obstruction.

The rare patient with volvulus of the transverse colon should also be treated by operative reduction and resection in two stages. Resection with delayed anastomosis is indicated in the presence of irreversible strangulation.

Acute cecal volvulus is so likely to recur following simple detorsion that the mobile cecum should probably always be fixed to the abdominal wall. In the occasional instance of early simple obstruction with minimal distention and edema of the bowel, suture fixation of the cecum to the peritoneum of the lateral abdominal wall is permissible. Routine cecostomy following detorsion is a safer procedure because it results in decompression plus fixation of the obstructed bowel. The patient with a gangrenous cecal volvulus is usually so gravely ill that right colectomy and ileotransverse colostomy are attended by a prohibitive mortality. Exteriorization resection is less dangerous.

In 25 per cent of the patients seen at Charity Hospital with carcinoma of the colon complete obstruction is present at the time of admission. The corresponding figures for the Lahey Clinic and the Mayo Clinic are approximately 2 per cent and 5.6 per cent, respectively, figures probably reflecting a different type of surgical practice.

There were 100 patients with acute large bowel obstruction due to carcinoma, and 42 of them died. The diagnostic and therapeutic errors contributing to this high mortality are being carefully analyzed, and the resultant findings will form the basis of a separate report. The major factors responsible for this excessive mortality in acute malignant colic obstruction may be briefly listed as follows: (1) failure to appreciate the multitude of differences between large and small bowel obstructions; (2) delay in decompression; (3) inadvisable abdominal exploration; (4) ill-advised primary resection; and (5) technical errors.

It is generally accepted that acute malignant obstruction of the large bowel is a disease requiring the earliest possible surgical attack, because the relief of intracolonic pressure is the primary factor in protecting the patient from death. This implies prompt, effective, surgical decompression in all cases.

The mortality in relation to the types of therapy is shown in Chart 4.

A mortality rate of 85 per cent occurred in the group of 13 patients treated conservatively. Nonoperative intestinal intubation is a valuable adjunctive measure in the management of intestinal obstruction, but its abuse is a major factor in the continued high mortality of the disease. The employment of suction as the sole mode of decompression is absolutely contraindicated in acute malignant colon obstruction, because there usually exists a closed-loop type of obstruction between the competent ileocecal valve proximally and the tumor distally. Moreover, this closed-loop large bowel obstruction with progressive distention of the proximal colon becomes essentially a strangulated obstruction.

Detailed discussions of the choice of operation for acute malignant large bowel obstruction have been presented in recent years.

Colon resection in the presence of acute obstruction is dangerous. In the present series, primary resection of an acutely obstructing colon carcinoma was performed 10 times with 7 deaths. This mortality of 70 per cent is to be contrasted with the mortality of 8 per cent which occurred in the patients with acutely obstructing colon carcinoma who survived a primary surgical decompression and later had elective resections.

In the past, most surgeons have considered cecostomy the procedure of choice for decompression of the distended colon. The mortality following cecostomy is high because of the near impossibility of aseptic decompression and the difficulty of complete delivery of the cecum in the presence of marked distention. The procedure has other disadvantages. The mortality of cecostomy in the present series was 42 per cent (Chart 4). Wangensteen states that the mortality at the University of Minnesota Hospital is almost 50 per cent.

In recent years many surgeons have concluded that the operation of choice in acute obstructing carcinoma of the left colon is a simple loop, right transverse colostomy. Transverse colostomy was performed in 16 cases with only 2 deaths, a mortality of 12.5 per cent. Analysis of the 52 cases in which proximal surgical decompression was done for

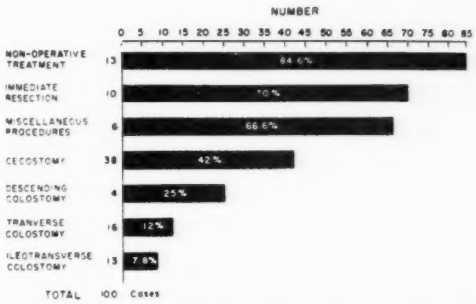

Chart 4. The mortality in relation to the type of therapy in 100 cases of acute intestinal obstruction due to carcinoma of the colon.

acute malignant sigmoidal obstruction indicated that cecostomy was performed in 20 instances with a mortality rate of 45 per cent, while transverse colostomy was utilized in 8 cases with a mortality of 12.5 per cent. Fallis reported a mortality of 3.8 per cent in 52 patients having transverse colostomy for acute left colon obstruction.

The choice of operation for obstructing carcinoma of the right colon depends upon the location of the tumor and the competency of the ileocecal valve. Cecostomy or ileotransverse colostomy may be employed. If the tumor is situated in the distal ascending colon, the hepatic flexure, or the right half of the transverse colon, a cecostomy is in order. In the presence of an obstructing cecal carcinoma an ileotransverse colostomy is a useful procedure, provided the ileocecal valve is incompetent, the ileum is not greatly distended, and the patient's general condition is satisfactory. Ileotransverse colostomy was performed in 13 patients with 1 death. If the ileocecal valve is competent the resulting closed-loop obstruction will not be relieved by the internal decompression of an ileotransverse colostomy, and some type of additional decompression is required. This decompression of a closed-loop cecal obstruction can be accomplished by completely dividing the ileum, effecting an ileotransverse colostomy, inserting a large catheter through the distal ileum into the distended cecum, and, finally, by bringing the distal ileal stump out through the abdominal wall as a mucous fistula.

General abdominal exploration should be avoided in the presence of acute malignant colic obstruction. In most instances careful clinical and roentgenographic examinations (including a cautiously administered barium enema) will make possible a correct preoperative diagnosis relative to the site and etiology of the obstruction, and render surgical exploration unnecessary. The early relief of intracolonic pressure is the primary factor in protecting the patient from death. This should be done by surgical decompression, with minimal manipulation and without exploration.

SUMMARY

An analysis of 205 cases of acute large bowel obstruction has been presented. The mortality was 32.7 per cent.

The major factors responsible for this excessive mortality have been listed.

Some of the basic principles relating to the treatment of acute colic obstruction have been re-emphasized.

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PANCREATIC CYSTS

Principles of Treatment

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ONE of the complications of acute pancreatitis is the formation of a pancreatic cyst. Among the unique characteristics of such cysts is the likelihood of their attaining a very large size. Surgical management advocated has been by the following diverse procedures: (1) Marsupialization or drainage by catheter. This is a safe procedure, but often leads to the formation of a cutaneous pancreatic fistula which may persist for months and even years, with all its attendant difficulties. (2) Anastomosis to the stomach or jejunum. Good results have been reported by this method. Its outstanding feature is that the formation of a cutaneous pancreatic fistula is obviated. (3) Excision of the cyst. This procedure is usually reserved for cysts springing from the tail of the pancreas and includes removal of a portion of the pancreas distal to the cyst. Attachment of the spleen or left kidney to the cyst wall may seriously complicate the surgical procedure. Leakage of pancreatic juice and lymph (resulting from injury of the large lymphatic trunks draining into the cisterna chyli) may cause severe postoperative difficulties.

Since the pancreas lies retroperitoneally, necrosis of, and hemorrhage from, the body or tail of the pancreas will result in a collection of necrotic tissue, blood, and pancreatic juice in the space between the left posterior abdominal wall and the peritoneum (Fig. 1). This space is easily distensible as experience with perirenal air insufflation indicates. Although the chemical inflammation during the height of the attack is no respecter of fascial planes, involving the kidney, spleen, stomach, and colon in the inflammatory process, the exudate left behind after the acute process subsides is confined to a definite space. As is actually found by observation, fluid accumulated in this space is limited in its spread by the spine and aorta on the right, by the diaphragm above, by the spleen, kidney, and descending colon on the left, and by the root of the sigmoid mesocolon below. It may also spread anteriorly by dissecting between the leaves of the transverse mesocolon and the gastrocolic omentum. Occasionally, the exudate may become trapped at this latter point and, after absorption of the retroperitoneal fluid, may be left behind as a mesenteric cyst or abscess.

Following an attack of severe pancreatitis with necrosis, the retroperitoneal exudate is usually absorbed and leaves no residue. However, in some cases, the necrotizing process in the pancreas may involve one or more pancreatic ducts, which then continue to pour pancreatic juice into the retroperitoneal space. The pressure of pancreatic secretion will maintain and extend the size of the cyst. The walls thicken, and this together with resistance to further extension of the surrounding structures will balance the intraductal pancreatic juice pressure and limit the size of the cyst. The resulting structure is then a pseudocyst, connected to the pancreatic duct system at one or more points, which may or may not close subsequently.

The situation in the head of the pancreas is somewhat different. Although small pseudocysts can be formed in the space between the pylorus and superior mesenteric vessels, the usual cysts found in the head are true cysts. That is, necrosis of pancreatic tissue

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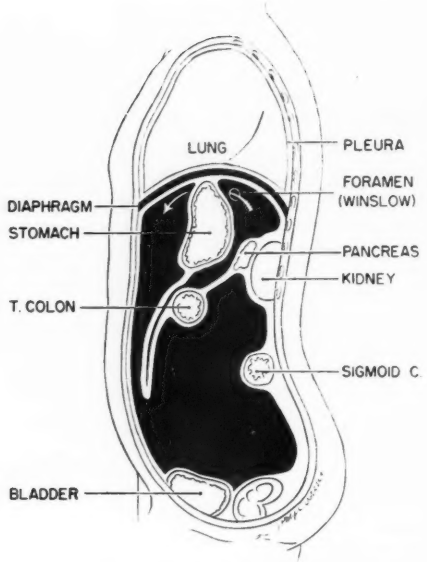

Fig. 1. Sagittal section through the left nipple line shows in rough diagrammatic manner the retroperitoneal space in which the pancreas lies. Exudate following acute inflammation will surround the capsule of the kidney and spread down as far as the sigmoid mesocolon. Upward spread will be halted at the diaphragm. The exudate may spread anteriorly between the leaves of the mesocolon as well as the gastrocolic omentum.

around the ducts of the uncinate process permits these ducts to expand as a result of pancreatic juice pressure and accumulation of mucoid secretion. The pancreatic tissue is gradually compressed and destroyed, and the cyst wall becomes hard and leathery. Its extension is limited by the pylorus and duodenum above and by the superior mesenteric vessels below. At times these vessels become intimately incorporated into the wall of the cyst.

The course of events already described and the concept that inflammatory pancreatic cysts develop, enlarge, and persist because of leakage of pancreatic juice from ruptured ducts has been developed over a period of years. Since the intraductal pancreatic pressure is a reflection of the resistance to flow created by the sphincter of Oddi, it would seem that the definite treatment of pancreatic cysts and fistulas should include, or be, section of the sphincter of Oddi. The following cases illustrate the development of this concept.

Case 1. J.G. (Bellevue Hospital, No. 906-48) was a 36 year old male admitted to the psychiatric division of Bellevue Hospital on February 24, 1948 in a semistuporous condition apparently due to insulin hypoglycemia. He had suffered attacks of severe epigastric pain radiating to the back for a period of 11 years. In 1940 an operation for obstructive jaundice (cholecystostomy and drainage of a pancreatic cyst) was performed. After 2 years the attacks of severe epigastric pain recurred and he became a morphine addict. In 1945, at another hospital, following studies which indicated marked diminution of pancreatic function, an attempt to do a pancreatectomy was abandoned and a splenectomy and drainage of a pancreatic cyst was carried out. He developed a persistent pancreatic fistula and attacks of epigastric pain recurred. Also, after this operation, a pancreatic-colic fistula was demonstrated but this apparently closed. At about this time, 1945, the patient developed diabetes for which he required 40 units of insulin a day. He continued to have attacks of severe pain associated with paralytic ileus on occasion.

Studies at Bellevue Hospital revealed a severe diabetes (glucose tolerance curve 173, 235, 333, 308 milligrams per cent blood sugar at ½ hour intervals). Injection of the pancreatic fistula with diodrast visualized part of the pancreatic duct and showed free communication with the duodenum. Further roentgen ray studies revealed a normal functioning gallbladder as well as calcification in the head of the pancreas (Fig. 2). He required frequent injections of demerol for pain and to alleviate morphine withdrawal symptoms.

At operation on April 5, 1948, the stomach, duodenum, and colon were found to be adherent to the liver. The gallbladder was surrounded by dense adhesions. The pancreatic fistula led to the body of the pancreas which was thickened and fibrosed, and the head was hard, irregular, and enlarged. Many large veins coursed around and over the gastrohepatic omentum, duodenum, and pancreas. The common duct was located only after a cholangiogram was done through the cystic duct following removal of the gallbladder. The common duct was wide above and tortuous and narrow in its passage behind the head of the pancreas. The pancreatic duct was not visualized. The common duct was opened and a fine probe passed into the duodenum. The duodenum was opened and the sphincter of Oddi was cut transduodenally over the probe. The pancreatic duct was seen to empty into the common bile duct 4 millimeters above the papilla, thus proving the presence of a common passageway. A fine catheter was passed into the duodenum, through the bile duct and brought out at the lateral angle of the wound. The pancreatic fistula was excised. The opening which remained

Fig. 2. Case 1. Gallbladder fills normally. Calcification which is indicated by the arrow is present in the head the pancreas. The tube lies in the cutaneous pancreatic tula.

Fig. 3. Case 1. Postoperative cholangiogram showed ready entrance of diodrast into the duodenum. The biliary tract above the enlarged head of the pancreas is markedly distended. The tube (arrow) lies in the distal part of the pancreatic duct and protrudes through a gastropancreatic anastomosis.

the main pancreatic duct was anastomosed to e overlying stomach over a small rubber tube. holangiograms taken 2 weeks after operation owed ready entrance of the contrast medium into e duodenum. The small tube over which the ncreatic duct was anastomosed to the stomach uld be seen (Fig. 3). Subsequent roentgenogram owed that the tube had passed. He has been ymptomatic since discharge, and the pancreatic tula has remained closed. He has gained 12 unds and requires 30 units of insulin daily. He no longer an addict.

It was noted that this patient had a nooth convalescence. There was no evience of leakage of pancreatic juice or of bphrenic accumulation on the left side. he thought was that the sphincterotomy d reduced the pancreatic intraductal pres- re and enabled the gastropancreatic fistula heal readily. This concept was reinforced by the observation that the jejunopancreatic astomosis, in cases of carcinoma of the ad of the pancreas treated by the Whipple peration, never leaked or gave any trouble. In such cases the whole sphincter mechanism is removed along with the head of the pancreas. The same idea was reinforced by the next case.

Case 2. W.C. (Bellevue Hospital, No. 334448-50) was a 47 year old male who was admitted on May 5, 1950, 3 days after the onset of severe epigastric pain, vomiting, and abdominal distention. He was treated by gastric suction, atropine, and penicillin. Within a few hours his pain disappeared and the next day the abdominal distention subsided. The serum amylase was found to be 30 milligrams per cent. He was placed on a fat free diet, but before any investigations could be carried out to determine the diagnosis he left the hospital against advice. He returned for further examination on May 31, 1950. Although he was asymptomatic, examination revealed a large epigastric mass. A swallow of barium to fill the stomach outlined a large pancreatic cyst (Fig. 6). A secretin test showed marked impairment of pancreatic function (total volume 92 cubic centimeters; total bicarbonate 48 cubic centimeters; total amylase 110 units). Mild diabetes was also present. At operation, June 15, 1950, a chronically diseased gallbladder full of stones was found; the pancreas was hard and fibrosed, and below it in the left lumbar gutter a large cyst was palpated. A cholangiogram showed reflux into the pancreatic duct (Fig. 4). A transduodenal sphincterotomy was done. The pancreatic duct was located 4 millimeters above the papilla into which a plastic tube was inserted and a pancreatogram performed (Fig. 5). The visualization of the tissues of the tail of the pancreas indicated that an acute inflammatory process involved that part of the pancreas. The pancreatic tube was left in situ, and passed up the common duct alongside the T tube which had been inserted into the common bile duct. After closure of the duodenum, the cyst which pointed between the stomach and transverse colon was opened. About 2 liters of purulent material were evacuated. The tail of the pancreas, which projected into this cyst like a finger, was inflamed and covered with necrotic tissue. A soft tube was placed into the cavity and the abdomen closed.

Purulent material drained from the cyst, but there was no leakage of pancreatic juice, although the plastic tube lying in the pancreatic duct drained 1,200 to 2,000 cubic centimeters of pure juice daily. The drainage tube in the cyst was removed in 4

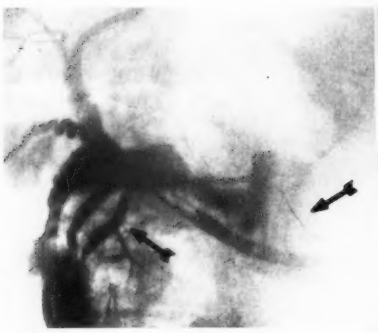

Fig. 4.

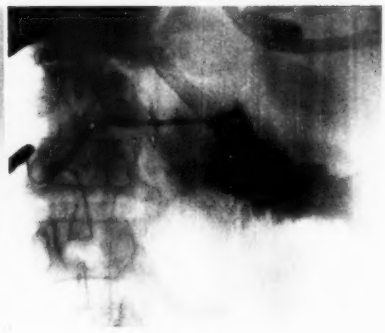

Fig. 5.

Fig. 6.

Fig. 4. Case 2. Operative cholangiogram shows reflux into the pancreatic duct as far as the tail (arrows). The pancreatic duct due to back pressure produced by a spastic sphincter is as large as the common bile duct.

Fig. 5. Case 2. Operative pancreatogram visualizing the pancreatic duct. The tissues of the tail of the pancreas, which protruded into the cyst, are completely visualized. The permeation of the diodrast into the tissues is due to loss of semipermeability as a result of acute inflammation.

Fig. 6. Case 2. A large cyst is seen pressing upward and displacing the stomach filled with barium. This exposure was taken with the patient lying down.

weeks. By that time the cyst had contracted leaving no cavity except the tract around the tube. This sinus closed within a day. The T tube and pancreatic tube were then removed, and he was discharged in good condition. He has remained well since, has gained 27 pounds in weight, and is fully employed. His present condition is satisfactory except for a mild diabetes and recurrent furuncles of the neck.

In this case the impression was gained again that the reduction in pancreatic duct pressure achieved by sphincterotomy had hastened the complete closure of the cyst. In the next case a different set of circumstances was present.

Case 3. W.K. (University Hospital, No. K47315) was a 40 year old bartender with an 8 year history of recurrent attacks of severe epigastric pain radiating to both upper quadrants and to the back, accompanied by vomiting. Thorough investigation in 1944 revealed no objective findings and he was treated for duodenal ulcer. The attacks persisted, growing more severe, and in the past year occurred 5 times. Each attack lasted 5 to 10 days. During a recent episode slight jaundice was noted and a roentgenogram at this time revealed widespread calcification of the pancreas (Fig. 7). Roentgenographic examination with barium in the stomach showed the presence of a cyst in the head of the pancreas pressing the pylorus downward (Fig. 8). At operation April 18, 1951 a large cyst was found occupying the head of the pancreas, the remainder of which was markedly enlarged and hard throughout. The gallbladder was thin-walled but surrounded by dense adhesions. Over the gallbladder, gastrohepatic omentum, duodenum, and head of the pancreas coursed large distended veins. A cholangiogram through the cystic duct revealed a narrowed tortuous common duct. A Bâkes dilator was passed through the cystic duct and down the common duct into the duodenum. After a No. 5 dilator had been passed, a sphincterotome was inserted and the sphincter of Oddi sectioned endocholedochally. The gallbladder was then removed and the cystic duct tied. The cyst was then aspirated with a large needle. It contained about 200 cubic centimeters of mucoid, a somewhat milky fluid. Diodrast was then injected and a roentgenogram taken to demonstrate its extent (Fig. 9). A 5 centimeter opening was made into the dome of the cyst. Brisk bleeding, controlled with diffi-

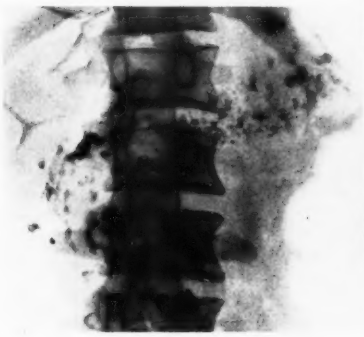

Fig. 7.

Fig. 8.

Fig. 7. Case 3. The whole pancreas is outlined by innumerable calculi.

Fig. 8. Case 3. Examination of the stomach with barium showed marked displacement downward of the pylorus due to a cyst in the head of the pancreas.

Fig. 9. Case 3. Injection of diodrast after evacuation of the contents of the cyst visualized its extent. The calcifications in the pancreatic tissue (arrows) show upward displacement of the head and neck of the pancreas.

Fig. 9.

culty, was encountered. The superior mesenteric vessels appeared to be incorporated into the inferior wall of the cyst which was hard and leathery. The jejunum was brought up through a rent in the mesocolon and anastomosed to the cyst at a distance of 50 centimeters from the ligament of Treitz. The abdomen was closed without drainage.

Postoperative recovery was without incident and he gained about 15 pounds in weight and is now working. However, he has had 2 episodes of painless massive upper gastrointestinal bleeding, presumably as a result of the portal varicosities which appear in such cases to be localized around the duodenum and gastrohepatic omentum. These bleeding episodes occurred after alcoholic drinking bouts. There was no evidence of esophageal varices on repeated roentgenographic examination of the lower end of the esophagus.

The presence of a large indurated cyst in the head of the pancreas in this patient excluded the possibility of treatment by drainage alone. Resection of the cyst with the head of the pancreas would have been an extremely hazardous and probably an impossible procedure due to the intense fibrosis which welded the head of the pancreas, the duodenum, the portal vein, and the superior mesenteric vessels into one solid mass. Cystojejunostomy was the only possible procedure. At the same time, sphincterotomy abolished the attacks of severe epigastric pain and stopped the progress of the disease.

The next case in which a pseudocyst was drained through the pancreatic duct by means of sphincterotomy gave us remarkable insight of the pathologic process in its involution.

Case 4. S.L. (Bellevue Hospital, No. 30931-52) was a 37 year old male who was admitted to another hospital with a 1 week history of severe epigastric and left upper quadrant pain accompanied by vomiting. A diagnosis of acute pancreatitis was made. While under treatment he became psychotic and was transferred to Bellevue Hospital on March 12, 1952. Under treatment by gastric suction, atropine, and intravenous fluids and electrolytes, including a large amount of potassium, his psy-

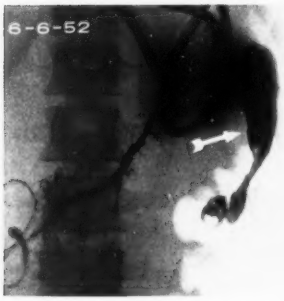

Fig. 10.

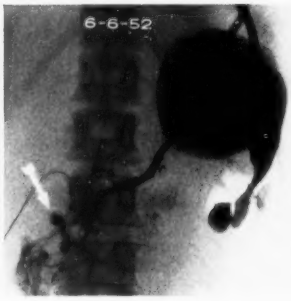

Fig. 11.

Fig. 12.

Fig. 10. Case 4. Pancreatogram 1 day postoperatively visualized the whole pancreatic duct which was apparently in free communication with the retroperitoneal space (arrow) in the left lumbar gutter.

Fig. 11. Case 4. Continued injection of diodrast visualized a large round pancreatic cyst. The blind dilated end of the accessory pancreatic duct (arrow) is clearly shown.

Fig. 12. Case 4. Anterior displacement of the stomach by a large cyst is clearly visualized on a lateral view preoperatively.

Fig. 13. Case 4. Five minutes after the injection of diodrast was discontinued, the pancreatic duct was shown to be free of diodrast. The pancreatic cyst and its extension into the left lumbar gutter was still clearly visualized.

Fig. 14. Case 4. Three hours later the diodrast had disappeared from the left lumbar gutter but still outlined the cyst. Two days later a flat plate of the abdomen showed complete disappearance of the diodrast.

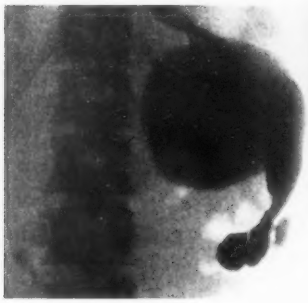

Fig. 13.

Fig. 14.

chosis and severe symptoms disappeared. A mass was palpated in the epigastrium. A swallow of barium outlined the stomach and demonstrated this large mass displacing the stomach anteriorly (Fig. 12). The urine contained some sugar but this disappeared in a few days. Bilateral active tuberculosis was found to be present in both apices. After extensive preparation during which the epigastric mass appeared to increase in size, operation was performed June 5, 1052. The gallbladder was edematous and thickened due to a pericholecystitis and was surrounded by many fresh adhesions. No stones were present. The pancreas was hard and indurated. Just below the tail and body a firm acutely inflamed mass which included the stomach, spleen, and transverse colon was found. The tissues were friable and bled easily. No area could be found which would indicate the pointing of a cyst anteriorly. No attempt at cholangiographic studies was made. The cystic duct was opened about 1 centimeter above its junction with the common duct. A No. 3 Bâkes dilator was passed to the

Fig. 15.

Fig. 16.

Fig. 15. Case 4. Pancreatogram taken 13 days after operation visualized the pancreatic duct, failed to visualize the cyst. The retroperitoneal space in communication with the pancreatic duct was markedly shrunken in size (arrow).

Fig. 16. Case 4. A lateral view still showed anterior displacement of the stomach by a large round mass. The pancreatic duct (arrow) curving around this mass is clearly shown.

Fig. 17. Case 4. A pancreatogram taken 28 days after operation visualized the pancreatic duct but failed to visualize either the pancreatic cyst or the retroperitoneal left lumbar space. The biliary tract is filled by reflux from the duodenum. The stub of the cystic duct (arrow) through which the plastic tube was inserted is shown.

Fig. 17.

pilla of Vater where it was arrested. The anterior wall of the duodenum was opened over the pinting probe for a distance of 1.5 centimeters. The papilla was pushed through this duodenal opening and sectioned. The pancreatic duct ostium was present inside the ampulla 5 millimeters above the tip of the papilla. A plastic catheter which had been passed down the cystic duct was then inserted about 6 centimeters up the pancreatic duct. The duodenum was closed and the cystic duct tied firmly around the catheter, which was brought out through a stab wound. The abdomen was closed without drainage. No attempt was made to drain the pancreatic cyst since the patient's condition was precarious, no evident point of drainage was present, and finally because it was believed to be unnecessary.

The postoperative course was smooth. After the third day the patient drank the pancreatic juice secreted through the plastic tube, mixed with fruit juices and ice; he gained weight rapidly, and the epigastric mass slowly disappeared. After 1 month he was transferred to the tuberculosis ward where he gained 20 pounds in weight. His pulmonary lesions improved rapidly, and he was finally transferred to a convalescent hospital.

X-ray studies during the postoperative period were illuminating. On the first postoperative day, diodrast was injected into the pancreatic tube. The pancreatic duct was visualized and then the diodrast was seen to run down the left lumbar gutter (Fig. 10). Further injection of diodrast filled out a round space which appeared to be a cyst (Fig. 11). Ten minutes after the injection was discontinued, the pancreatic juice flow had washed out the diodrast, but the cyst and retroperitoneal space were still visualized (Fig. 13). That same afternoon the cyst was still visible, but the diodrast in the left lumbar gutter had been resorbed (Fig. 14). Two days later nothing could be seen.

Twelve days later, on June 18, 1952, the patient was again roentgenographed. The whole pancreatic duct was visualized. Some diodrast ran into the left lumbar gutter, but the retroperitoneal space involved was definitely smaller (Fig. 15). A lateral view showed the cyst to be smaller, but still extensive (Fig. 16). On July 3, 1952 re-examination visualized the pancreatic duct but the left lumbar retroperitoneal cavity had apparently closed since no diodrast entered it (Fig. 17). Since some of the diodrast had refluxed back into the

Fig. 18.

Fig. 19.

Fig. 20.

Fig. 18. Case 4. These views were taken with the patient in the erect position in order to overcome interference from the diodrast lying in the cardia of the stomach. It was now seen that a small space, in communication with the pancreatic duct, was still present below the cyst.

Fig. 19. Case 4. A lateral view in the same position demonstrated that this fine space almost surrounded the cyst (arrows). The cyst had now shrunk to a very small diameter and the stomach was no longer displaced anteriorly.

Fig. 20. Case 4. This was the final pancreatogram taken before removal of the plastic tube 46 days after operation. The pancreatic juice was flowing so strongly that only the terminal part of the pancreatic duct (arrow) was visualized. The diodrast was washed into the intestinal tract.

stomach from the duodenum and obscured the tail of the pancreas, it was decided to take some views in the erect position. This showed the presence of a small space, like a sliver of moon, still communicating with the pancreatic duct (Fig. 18). A lateral view demonstrated how extensively the cyst had shrunk (Fig. 19). The fine space around it was clearly outlined by the diodrast. On July 21, 1952 the last pancreatogram was done. At this time the pancreatic juice was flowing so strongly that only the terminal part of the pancreatic duct was outlined (Fig. 20). At this point the tube was removed without any trouble and the patient discharged to the tuberculosis service.

This case was instructive in that it showed by means of serial pancreatograms the gradual disappearance of a pancreatic cyst, once the intraductal tension of pancreatic secretion was reduced by sphincterotomy. Complete demonstration of this principle can be illustrated in the following case in which a cutaneous pancreatic fistula persisted after drainage of a pancreatic cyst.

Case 5. J.B. (University Hospital, No. K60910) was a 64 year old male who was admitted to another hospital in June 1952 with a 4 day history of severe periumbilical pain, accompanied by vomiting, abdominal distention, and fever. A large epigastric mass was palpable. A hemorrhagic cyst lying retroperitoneally below the pancreas was drained on July 30, 1952. Large amounts of brown purulent fluid flowed through the tube for a month following which he was discharged with the tube in situ. Small amounts of this fluid continued to drain, and, in addition, the patient suffered 3 attacks of severe epigastric pain, abdominal distention, and vomiting. When first seen by us on September 27, 1952, he was in obvious pain and was markedly dehydrated as a result of continuous vomiting for 3 days. Tenderness was present in the epigastrium and beneath the left costal margin. A tube draining a small amount of brownish fluid was present on the right side of the abdomen. He

Fig. 21.

Fig. 22.

Fig. 21. Case 5. Diodrast injected through a tube lying in the cutaneous pancreatic fistula outlined an irregular space beneath the body and tail of the pancreas, visualized part of the pancreatic duct system and emptied readily into the intestinal tract.

Fig. 22. Case 5. A lateral view showed that this space extended into the left lumbar gutter.

Fig. 23. Case 5. Operative pancreatogram showing reflux into the pancreatic duct as far as the tail. The tube lying in the cutaneous pancreatic fistula extends to this area.

Fig. 23.

as admitted to the University Hospital and eated by nasal gastric suction, atropine, and intravenous fluids. The tenderness subsided rapidly. iodrast was injected into the tube and revealed e presence of an irregular cavity behind the body d tail of the pancreas. This cavity communiated with the pancreatic duct, through which aparently the diodrast entered the small intestine adily (Figs. 21 and 22). Until operation on Octber 8, 1952, the tube continued to drain small uantities of fluid. At operation the gallbladder as found to be surrounded by dense adhesions d the wall was thickened and fibrosed, but contained no stones. The head and body of the pancreas were hard and indurated, with fibrosis extending as far as the tail. A cholangiogram showed a dilated common duct with reflux up the pancreatic duct as far as the tail. The tip of the tube draining the pancreatic fistula lay exactly under the tail of the pancreas (Fig. 23). The cystic duct was opened and a small Bâkes dilator passed down the common duct into the duodenum. Transduodenal sphincterotomy was performed. The pancreatic duct ostium was located in the ampulla of Vater 4 millimeters above the papilla. Before closing the duodenum, saline was injected through the pancreatic fistula tube. It was noted that it escaped into the duodenum through a fistula in the posterior wall of the second part of the duodenum. No attempt was made to close this internal fistula or to dissect out the pancreatic fistula. The cystic duct was tied off after withdrawing the probe, and the abdomen closed without drainage except for the tube which lay in the fistulous tract.

Recovery was rapid and after the third postoperative day there was very little leakage of fluid from the fistula. The tube was gradually shortened. The patient was discharged 10 days after operation and the tube removed on the fifteenth day. The fistula closed completely within 2 days. The patient has been well since and has returned to work.

DISCUSSION

The relation of pancreatitis to the production of pancreatic cysts has been well established. The concept that recurrent pancreatitis in the majority of cases results from the retrojection of bile into the pancreatic duct has been supported by our experience. This event can occur only if the sphincter of

Oddi is spastic and when the bile and pancreatic ducts join in a common ampulla above the papilla of Vater. The presence of this anatomic common passageway in our cases of pancreatitis and the good results achieved by sphincterotomy tend to support this concept.

It, therefore, follows that patients, in whom cysts of inflammatory origin are present, must have, either at intervals or continuously, spasm of the sphincter of Oddi. Such a condition would tend to perpetuate or increase the size of the pancreatic cysts. Drainage of these cysts would tend to persist for long periods of time because the pancreatic intraductal pressure would be higher than normal as a result of sphincter spasm. For the same reason attacks of pancreatitis may recur even in the presence of a draining pancreatic fistula, as is illustrated in Cases 1 and 5, as well as from many reports in the literature. Successful treatment of a pancreatic cyst by drainage does not prevent recurrence of attacks of pancreatitis and formation of new cysts. This happened in a case reported in this article (Case 1). Therefore, sphincterotomy should not only help in the treatment of an inflammatory pancreatic cyst but also, by removing the basic cause of pancreatitis, should prevent further attacks of the disease.

Although cystogastrostomy and cystojejunostomy have yielded good results, it does not seem to be a good surgical principle to anastomose the gastrointestinal tract to a retroperitoneal space. From our experience it does not appear to be necessary except in cysts of the head of the pancreas in which the cyst wall, probably a dilated duct, is hard as well as rigid and cannot be obliterated.

Since an attack of acute pancreatitis with marked pathologic changes can occur with very few or no overt clinical symptoms, it is not surprising that pancreatic cysts are found without a previous history of gastrointestinal disease. Such cysts, unless of congenital origin or due to an adenomatous growth, must have arisen as a result of an attack of acute pancreatitis.

Traumatic injury of the pancreas may produce necrosis of pancreatic tissue and rupture of the ducts. Since the pathologic process following such injury is similar to that following an attack of acute pancreatitis, any cyst that may result should be treated on similar principles.

CONCLUSIONS

1. Pseudocysts of the pancreas, of inflammatory origin, should be treated by drainage and by section of the sphincter of Oddi. This will not only cure the cyst but will also prevent the recurrence of attacks of pancreatitis.

2. Persistent cutaneous pancreatic fistulas, resulting from drainage of a pancreatic cyst, should be treated by sphincterotomy.

3. Cysts of the head of the pancreas, because ducts are frequently a component, should be treated by cystojejunostomy and sphincterotomy.

SARCOMAS OF THE BREAST

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SARCOMAS of the breast, which constitute about 1 per cent of malignant mammary tumors, are of clinical importance because they offer a more avorable prognosis than other malignant umors of the breast. Breast sarcomas may row slowly for long periods and tend to re-ain localized within the breast parenchyma. Ialignant involvement of regional lymph odes has been reported in less than 3 per ent of cases by Gross and Geist and Wilen-ky. Despite their inherent malignancy, sur-ical treatment of breast sarcomas has been ttended with considerable success.

The sudden transition of a small, painless reast tumor of long standing to a rapidly rowing lesion often indicates a sarcoma de-eloping in a pre-existing fibroadenoma. This ype, termed adenosarcoma by Geschickter, ontains epithelial elements and is found only the breast. Another type, the pure spin-le-cell sarcoma, is probably a closely related umor, since a recurrence of an adenosarcoma ay take this form. The latter type may also rise from blood vessels, nerve sheaths, or ven fat, and may contain cartilage or bone. Iyxomatous characteristics are often pres-nt in the largest of such sarcomas. One ystic sarcoma of the breast weighing 20 kilo-rams has been reported by Velpeau (2). The unduly high incidence cited in early re-orts by Williams in 1893 may be due to he classification as sarcomas of such various ther lesions as melanoepithelioma, lympho-arcoma, benign giant intracanalicular myx-oma, and erroneously diagnosed anaplastic arcinoma.

Surgical procedures of varying extent have been followed in the removal of breast sar-omas. Geschickter recommended simple mastectomy with removal of the pectoral fascia. As a deterrent to local recurrence, Bloodgood advocated removal of the pectoralis major muscle in addition to simple mastectomy. Radical mastectomy has not been advised routinely in view of the infrequent lymph node spread. Since these connective tissue tumors are all relatively radioresistant, x-ray therapy has offered little in their treatment.

In the period from 1915 to 1951, of 1,291 patients with breast cancers observed at the University of California Hospital, 15 cases of primary sarcoma (or 1.2 per cent of the total) were encountered. All of the patients in this series were female. Their ages ranged from 15 to 67 years, the peak incidence occurring between 45 and 60 years of age. A review of these cases affords additional evidence as to some of the characteristics of these lesions and the effectiveness of surgical treatment.

The gross appearance of a breast sarcoma is usually that of a bulky tumor that tends to be locally invasive and locally recurrent (Fig. 2). There is rare involvement of the skin or nipple.

The manner of growth of breast sarcomas as manifested in our series was as follows: In 5 patients the duration of the tumor was 0 to 6 months; in 1 patient, 8 months; in 2 patients, 2 to 3 years; in 3 patients, 7 to 8 years; in 2 patients, 10 to 12 years; and in 2 the duration was not stated. It is evident that they may remain quiescent or localized for considerable periods. Of the 15 patients observed, 5 had been aware of a mass in the breast for as long as 7 to 12 years, while only 5 had sought medical advice within 6 months after discovering the tumor. It is apparent that spread to the regional lymph nodes is rare, since no involvement of lymph nodes was noted in any of our patients. Recurrence of the tumor in the axilla and shoulder region after radical mastectomy, which occurred in 1 instance, was probably due to

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a b

Fig. 1. a, The extent of the malignant involvement about the shoulder joint necessitated a shoulder girdle amputation. b, A simple prothesis worn beneath the patient's clothing restores the contour of the shoulder.

spread along fascial planes beyond the limits of dissection at the original operation. Even a recurrent tumor tends to remain localized, as was seen in 1 patient who had 4 local excisions over a 12 year period with no evidence of recurrence 2 years after the last wide excision.

Considerable variation in the rate of growth may occur. The factors influencing a change in growth as observed in the patients in our series indicated: pregnancy in 2 patients; hormone therapy in 1; biopsy in 1; incision into tumor in 2; and incomplete excision in 2 patients. In 2 cases, incision into the mass because of the mistaken diagnosis of abscess resulted in rapid proliferation and ulceration. Three patients noted changes in the character of their lesions incident to pregnancy or to hormone therapy for menopausal symptoms.

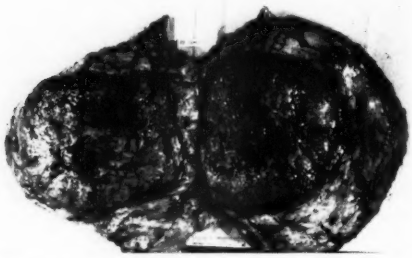

Fig. 2. Note the rather well circumscribed character of the tumor. A pseudocapsule of compressed breast parenchyma surrounds the lesion.

As Ewing has indicated, although the rate of growth may vary widely, rapid growth when once established is maintained. It is not unusual for a sarcoma to reach a tremendous size before definitive treatment is instituted. The largest tumor in our series measured 35 centimeters in diameter and manifested myxomatous characteristics.

Three types of sarcomas were present in our series: The majority of the lesions were fibrosarcomas (9 cases), some of which had myxoid elements. In 5 cases, microscopic study suggested that the sarcoma probably arose in a previously existing fibroadenoma. One tumor was a neurofibroma.

In the majority of cases, as indicated in Table I, surgical treatment, with application of the principle of wide excision of all involved and potentially involved tissue, afforded good results. Four of the patients in our series were treated by local excision, 3 by simple mastectomy, 6 by radical mastectomy, while 1 was treated elsewhere and 1 whose sarcoma was discovered at autopsy received no treatment.

The rarity of metastases, however, should not mask the malignant nature of these tumors, nor their virility on recurrence. The

TABLE I.—RESULTS OF TREATMENT

Treatment	No. of patients	Living and well			Died	Lost to follow-up
		1–4 years	5–9 years	10 yrs. or more		
Radical mastectomy	5	1	1	1	1 (operative death)	1
Radical mastectomy and shoulder girdle amputation	1			1		
Simple mastectomy	3		1	2		
Local excision	2			1		1
Multiple local excisions	2	1			1 (19 yrs. after surgery)	
Treatment elsewhere	1					1
No treatment	1				1 (discovered at autopsy)	

ourse of 2 of our patients affords striking vidence that the principle of adequate exision of malignant or potentially malignant issue is best applied to the original operative procedure.

The first of these, a woman aged 56 years, ad had an ulcerating mass in the upper uter quadrant of the right breast for 3 ears. Radical mastectomy done elsewhere as followed in 1 year by a recurrence of the yxofibrosarcoma in the right axilla. This ass was treated by local excision, but after 10 year period the tumor again recurred nd involved the axillary region and adjaent anterior shoulder area. An interscapulohoracic amputation was then necessary to radicate the lesion. It is now 7 years since he shoulder girdle amputation, and there is s yet no evidence of recurrence (Fig. 1).

Another patient, aged 49 years, was admitted to the University of California Hospital for the first time in August 1946. Seventeen years previously (1929), a small mass excised from the right breast was diagnosed histologically as a fibroadenoma. In 1933, a mass which recurred in the area of the biopsy scar was again reported to be a "nonmalignant tumor." In January 1945, the patient noted a small nodule in the previously treated area of the right breast. The mass grew rapidly after its discovery, possibly owing to the influence of a course of estrogenic hormones being self-administered by the patient for menopausal symptoms. The mass was excised by a simple mastectomy, plus removal of the pectoral musculature. The laboratory diagnosis at this time was myosarcoma. The tumor recurred locally again in May 1946, in August 1946, and in April 1947. In each instance wide local excision of the recurrent tumor was accomplished but to little avail, since the patient expired with a huge local recurrence involving the right upper arm and the adjacent chest wall in March 1948, 19 years after the first local excision had been performed.

It is evident that these patients underwent several incomplete surgical procedures with respect to the extent of the primary lesions.

SUMMARY

The observations gained from a study of 15 patients with breast sarcomas during a 35 year period at the University of California Hospital are presented.

Sarcomas of the breast tend to remain locally malignant for long periods before ultimate more rapid proliferation occurs. For this reason, adequate surgical removal at the time of initial surgery, preferably by radical mastectomy, in spite of the relative infrequency of spread to regional lymph nodes, must be considered as the procedure best suited to the treatment of such malignant growths.

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DELAYED PRIMARY CLOSURE OF KOREAN WAR WOUNDS

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SURGICAL experience during World Wars I and II led to the conclusion that, in general, delayed primary closure of wounds is the treatment of choice in battle incurred injuries. Since the close of World War II increasing effectiveness and usage of antibiotics have contributed to a decrease in complicating wound infections and allowed the surgeon greater latitude in his choice of procedures, within the limits of sound surgical principles. It is the purpose of this paper to define further these surgical principles and to report the author's experience in delayed primary closure of wounds incurred in the Korean conflict. Reference will be made to thorough and adequate débridement and to methods of closure without tension.

DÉBRIDEMENT

Adequate débridement of the wound is a prime essential to successful closure. This entails evacuation of bits of clothing, gravel, or dirt; excision of necrotic tissue down to reddish colored bleeding muscle; drainage of abscesses; and removal of metallic foreign bodies. One is concerned only with those foreign bodies within the wound tract. Those that are distant and require removal for definitive reasons must be approached through a separate incision, usually as an elective procedure and not concomitant with the débridement. It is most important to lengthen skin incisions or raise flaps in order to obtain adequate exposure. Attempted débridement through a small wound, without direct vision of extent of the pathologic condition, results in inadequate removal of necrotic tissue or foreign material and not infrequently leads to further tissue damage due to blind dissection. Moreover, trauma of major vessels with hidden aneurysms in the depths of the wounds has been missed because of inadequate exposure and inspection. A corollary to the requirement of adequate exposure is the use of a general anesthetic agent. In small, superficial, shallow wounds, local infiltration anesthesia may be acceptable, but in all other types of wounds general or regional anesthesia should be utilized. Following débridement, the wound should be thoroughly flushed with copious quantities of warm saline or water, to cleanse the area thoroughly of tiny remaining bits of extraneous material.

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CASE 1. (Figs. 1, 2, and 3.) The wound in the midportion of the left buttock measured 20 by 15 centimeters. The wound in the upper third of the lateral thigh over the trocanter measured 15 by 7 centimeters. The wounds were separated by a 20 centimeter flap of intact skin. They were débrided in Korea, but débridement had been inadequate, and when the patient was admitted to this hospital, 9 days after injury, the wounds were moderately dirty.

In order to débride this wound adequately, it was necessary to make a transverse incision at the base of the flap between the two wounds and reflect this 20 centimeter flap upward to expose the entire area. Burned and necrotic fascia lata was excised along with dead muscle. The posterior superior spine of the ilium was bared and small pieces of separated dead bone were removed. Closure was obtained by wide undermining of lateral and medial flaps and resuturing of the wound on the three aspects. Immobilization was obtained with a plaster hip spica. As seen in Figure 3, excellent healing was obtained although there was a 5 centimeter loss of the distal portion of the flap. This area healed by granulation. This wound could not have been adequately débrided nor properly treated without wide exposure.

CLOSURE WITHOUT TENSION

The application of the principle of closure without tension is probably the most important single factor in successful closures, and yet the one that I have seen most frequently violated. The usage of suture material to pull tissues together, rather than simply to approximate them, is a frequent cause of wound breakdown. Tissue necrosis is almost certain to result when there is an attempt on the part of the surgeon to effect the closure with a tight suture rather than cover the wound with a skin graft. It is far better to resort to grafting initially, and thus prevent additional trau-

Fig. 1.

Fig. 2.

Fig. 3.

Figs. 1 and 2. Case 1. Preoperative views. Medial wound measured 20 by 15 centimeters; lateral wound, 15 by 7 centimeters; intervening flap, 20 by 20 centimeters.
Fig. 3. Case 1. Eight weeks postoperatively.

ıa to the patient, multiple procedures, and ɔss of time.

The methods that are used to avoid tension re multiple, dependent on the part of the ɔdy involved and the shape and direction of ıe wound. Thus thigh and buttock wounds, ı general, lend themselves ideally to simple ɔsure when large medial and lateral flaps ın be developed. Undermining is usually ıfe for a distance of 12 to 14 centimeters be- ath each flap. If, however, the wound is ɔrizontally placed on the thigh so that supe- ɔr and inferior flaps are required, undermin- g is limited to approximately 5 to 6 centi- ıeters and this type of wound is usually best ɔsed by grafting. Leg wounds 8 centimeters r wider should usually be grafted, rather than eated by simple closure, since here again undermining is limited to approximately 5 centimeters. A decision as to choice of procedure, however, should be only tentative until final evaluation at the operating table. This is well demonstrated in Cases 2 and 3.

Case 2. (Figs. 4, 5, and 6.) This case involved a shrapnel wound of the left thigh, measuring 35 by 25 centimeters, complicated by gasoline burn. The wound was débrided in Korea, but inadequately, and the patient was admitted to hospital in Japan, 48 hours after injury.

A second débridement was done 48 hours after admission, or 96 hours after injury. This was followed by 4 days of preparation with massive wet pressure dressings and parenteral antibiotics. Hemoglobin level was brought to 12 grams.

Dermatome and free hand skin grafts were applied on the eighth day after wounding because of: (1) pain on dressing change and (2) the press of evacuation policy. (During this particular period all patients

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4. Case 2. Wound measuring 25 by 35 centimeters inadequately débrided.
Fig. 5. Case 2. Following second débridement and 4 days of wet pressure dressings.
Fig. 6. Case 2. Postoperative view. Wound closed with split grafts.

Fig. 7.

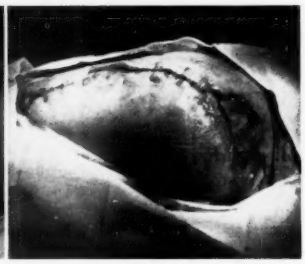

Fig. 8.

Fig. 9.

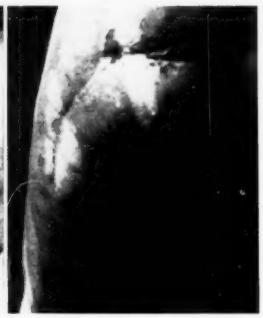

Fig. 10.

Fig. 7. Case 3. Wound measuring 25 by 35 centimeters after partial débridement in Korea.

Fig. 8. Case 3. Upon completion of surgery, lower 75 per cent closed by flap mobilization, upper 25 per cent closed by grafting.

Fig. 9. Case 3. At time of first dressing 5 days postoperatively.

Fig. 10. Case 3. Final result, 3 months postoperatively.

who required more than 30 days' hospitalization were returned to the United States.) Although several more days of wound preparation would have been ideal, a 75 per cent take of the grafts was obtained. This was increased to 90 per cent by application of refrigerated skin on the seventh postoperative day. This latter skin was saved from the original operative procedure. The patient was evacuated to the United States on the fourteenth postoperative day, with the wound 90 per cent closed. Note the margins left between the strips of skin and about the wound edges. This principle of noskin to skin closure is an excellent one in wounds that are not ideally clean.

Partial closure and graft. The method of partial closure and graft is an excellent approach to wounds that present a tension problem in a part of the involved area, whereas the remainder may be closed without tension by free mobilization of flaps. Leg wounds and ovoid shaped wounds in general frequently fall into this category.

CASE 3. (Figs. 7, 8, 9, and 10.) This case involved a 25 by 35 centimeter wound of the upper thigh and buttock complicated by gasoline burn. The wound was partially débrided in Korea and the patient was admitted to this hospital 3 days following injury.

Preoperative preparation consisted of 9 days of massive wet pressure dressings, during the last 4 days of which a layer of 300,000 units of penicillin in 5 cubic centimeters of saline was placed against the wound once daily. Hemoglobin was restored to 13 grams.

By means of wide undermining the lower 75 per cent of the wound was secondarily closed; the upper 25 per cent of the wound was grafted with a dermatome split graft, approximately .015 inch in thickness. In the preoperative plan of procedure complete grafting of this wound had been visualized. At the time of surgery, however, medial and lateral flaps were readily developed in the lower three fourths of the wound, and this portion was closed by approximation. The upper 25 per cent of the wound did not lend itself to development of flaps without tension; therefore, a graft was used for closure. Figure 10 shows the wound 3 months following surgery. The

Fig. 11. Fig. 12. Fig. 13. Fig. 14.

Fig. 11. Case 4. Twenty-five days after injury. Original delayed primary closure had broken down.
Fig. 12. Case 4. Twenty-two days postoperatively. Lateral flap had been shifted medially. Donor area was covered with split graft. Lateral view.
Fig. 13. Same as Figure 12. Posterior view.
Fig. 14. Same as Figure 12. Medial view.

patient was evacuated to the United States because of disability due to muscle loss and weakness.

If this case is compared with Case 2 it will be noted that the appearance of both wounds is strikingly similar and is due to a bursting of muscle through fascia. In Case 2, there was, in addition, a marked loss of skin, whereas in Case 3 there was a relatively small loss of skin.

Relaxing incision. The use of the so-called relaxing incision is another helpful procedure in relieving tension. In actuality, by means of the relaxing incision a double pedicle flap is outlined and shifted to cover the wound. The raw area is covered with a split graft. In dealing with flaps a good rule of thumb is that the length of the flap should be not more than 2 to 3 times the width. Long wounds, therefore, require relaxing incisions at a considerable distance from the wound edge, in order to allow for sufficient width. Failure to observe this principle will result in loss of parts of the flap, especially in the mid-portion where the blood supply is poorest.

Case 4. (Figs. 11, 12, 13, and 14.) The original wound in this patient measured 6 by 4 centimeters over the lower third of the tendo achillis. A delayed primary closure was done 8 days after injury with a breakdown of the wound due to tension. Figure 11 portrays the wound on admission to this hospital, following the unsuccessful result, when the wound measured 4 by 2 centimeters with the tendon exposed at the base.

Preoperative preparation consisted of parenteral antibiotics and 3 days of wet dressings.

The wound was completely excised to include portions of frayed tendon. Upon completion of dissection the tendon was free. A wide long double pedicle flap was shifted medially from the lateral aspect of the leg. This procedure provided flap coverage for the tendon and placed the suture lines at the margin of the wound to prevent adherence to the tendon proper. The raw area created by the flap shift was covered with a .018 inch dermatome graft, and an excellent take was obtained. The tension problem was completely obviated by the use of the double pedicle flap technique.

Closure of adjacent wounds. Closure of wounds adjacent to each other requires careful planning in order to prevent tension. The flap intervening between the two wounds can usually be undermined and mobilized in only one direction to cover one of the wounds. The second wound should be grafted. In other instances, the intervening flap may be long and narrow so that undermining in either direction may place the flap in jeopardy. In such instances it is better judgment to graft both wounds.

Case 5. (Figs. 15 and 16.) The right thigh wound measured 19 by 6 centimeters. The wound on the anterior aspect of the left thigh measured 22 by 10 centimeters; the wound on the medial aspect, 19 by 6 centimeters. The wounds were débrided in Korea and the patient was admitted to this hospital 6 days following wounding.

Preoperative preparation consisted of 4 days of wet dressings and parenteral antibiotics.

The right thigh wound presented no problem and was easily closed, without tension by undermining and coaptation of flaps, with No. 000 black silk and buried No. 80 cotton. Both wounds of the left thigh could not be closed without placing the intervening flap in jeopardy. The anterior wound was therefore

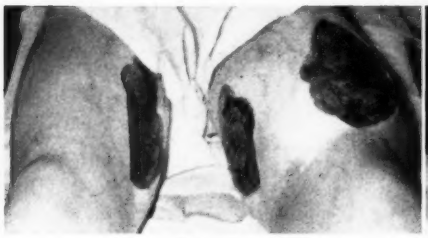

Fig. 15.

Fig. 16.

Fig. 15. Case 5. Preoperative view. Wound on anterior aspect of left thigh measured 22 by 10 centimeters; on medial aspect, 15 by 5 centimeters. Right thigh wound measured 19 by 6 centimeters on medial aspect.

Fig. 16. Case 5. Postoperative view, 10 days after surgery.

undermined and closed. The medial wound was grafted. Figure 16 depicts the result on the eighth postoperative day.

Closure by distant flaps. The closure of wounds by distant flaps is not a generally recommended procedure in the overseas theater. The immediate problem is the conversion of an open wound to a closed wound, and this is best done by the simplest and safest approach, which ordinarily does not include the use of distant flaps. The secondary problem of reconstructive surgery should be undertaken at a later date in the United States when circumstances are more favorable for reconstructive procedures. The calculated risks involved—infection, loss of portions of the distant flap, and the creation of a needless secondary deformity —are usually great enough, so that best judgment dictates that distant flaps not be used except under specific conditions. These conditions include the following: (1) the dividends to be gained are great, such as the preservation of viable tendon, nerve, or bone; (2) the wound site and adjacent area appear to be clean; (3) the surgical judgment, experience, and technique of the operator are of a high order; and (4) a local flap is impracticable or impossible. When these conditions can be fulfilled the use of a distant flap may well be justified. It is interesting to note that in the total of 1,020 cases reported in our statistical analysis, only 3 distant flaps were used. Contrawise, 42 local flaps were used for closure.

SUMMARY

A résumé is presented of the author's experience in the surgical care of soft tissue injuries incurred in the Korean conflict. Clinical summaries are recorded of cases demonstrating the surgical principles involved in delayed primary closure of these wounds. The principles of adequate débridement and closure without tension are emphasized. The methods employed to avoid tension are illustrated.

Statistical Analysis

Earlier in this paper were detailed the experiences of the author and his staff in delayed primary closures of Korean war wounds. In this portion of the paper a statistical analysis is presented of 1,020 consecutive wounds closed in accordance with the principles emphasized herein. The wounds were incurred during the period October 1950 through March 1952 and represent consecutive soft tissue closures performed by the author and his staff. No cases were discarded except those that involved wounds which were shallow, superficial, and measured under 3 by 1 centimeters. The tables are divided into series A and series B; the former representing 279 cases done by the author, the latter representing 741 cases performed by surgeons supervised by the author. These surgeons were 9 in number, 2 of whom did not have sufficient training to be classified by the Army as surgical specialists. Of the remaining 7, 3 were Board qualified, and 4 had a minimum of 18 months of formal training, but were not Board qualified. Eleven tables are presented, 6 of which detail statistics of informational value, 5 of which present figures from which conclusions may be drawn.

Table I is not a picture of the breakdown of all war wounds into various parts of the body

TABLE I.—NUMBER AND LOCATION OF WOUNDS

	Series A		Series B	
	No.	Per cent	No.	Per cent
Patients	226		539	
Wounds	279		741	
Upper extremity	49	30	111	15
Lower extremity	147	52	430	58
Other parts of body	83	18	200	27
Total	279	100	741	100

TABLE II.—LOCATION OF WOUNDS OTHER THAN EXTREMITIES

	Series A		Series B	
	No.	Per cent	No.	Per cent
Buttocks	32	38.5	96	48
Sacral and lumbar region	17	20.5	30	15
Anterior chest wall	4	5	18	9
Posterior chest wall	4	5	9	4.5
Anterior shoulder	6	7	14	7
Posterior shoulder			13	6.5
Neck	7	8	5	2.5
Face	8	10	6	3
Scalp	4	5	6	3
Abdomen	1	1	3	1.5
Total	83	100	200	100

TABLE III.—SITE OF LOWER EXTREMITY WOUNDS

	Series A		Series B	
	No.	Per cent	No.	Per cent
Thigh	57	39	254	59
Leg	72	48.5	139	32
Foot	10	6.5	12	3
Knee	4	3	3	1
Popliteal space	4	3	22	5
Total	147	100	430	100

but of those which lend themselves to secondary closure.

The number of upper extremity wounds, particularly those of the hand, was comparatively small (Table IV). Many more hand wounds passed through the hospital but these patients were evacuated to the United States for definitive reconstructive procedures.

TABLE IV.—SITE OF UPPER EXTREMITY WOUNDS

	Series A		Series B	
	No.	Per cent	No.	Per cent
Arm	12	24.5	51	46
Forearm	12	24.5	45	40.5
Hand	15	31	11	10
Elbow	4	8	4	3.5
Axilla	6	12		
Total	49	100	111	100

TABLE V.—SIZE OF WOUNDS

	Series A		Series B	
Smallest wound	3×1 cm.		3×1 cm.	
Largest wound	25×35 cm.		25×30 cm.	
	No.	Per cent	No.	Per cent
50 sq. cm. or less	193	69	584	79
51—100 sq. cm.	49	17	87	11
101—300 sq. cm.	30	11	60	9
Over 300 sq. cm.	7	3	10	1
Total	279	100	741	100

TABLE VI.—LENGTH OF TIME FROM WOUNDING TO ARRIVAL IN JAPAN

	Series A		Series B	
	No.	Per cent	No.	Per cent
1—3 days (0 through 72 hours)	146	52	211	29
4—6 days (73 through 144 hours)	99	36	380	51
One week or over	34	12	150	20
Total	279	100	741	100

Tables VI, VII, and VIII may be considered as a unit. Note the difference in percentage of débridement between series A and B. This difference obtained because approximately 20 per cent of the cases in series A were patients wounded during the November 1950 Communist push, including the Hamhung and Hungnam evacuations. Combat conditions did not permit débridements during that period. One might expect, therefore, that a greater number of earlier closures could be effected in series B than in series A. As seen in Table VIII, this was not so. The explanation of this apparent paradox is based on two

TABLE VII.—DÉBRIDEMENT STATUS ON ARRIVAL IN HOSPITAL IN JAPAN

	Series A		Series B	
	No.	Per cent	No.	Per cent
Débrided	133	48	689	93
Not débrided	146	52	52	7
Total	279	100	741	100

TABLE VIII.—LENGTH OF TIME FOR PREPARATION OF WOUNDS

	Series A		Series B	
	No.	Per cent	No.	Per cent
1—5 days	114	41	342	46
5—10 days	106	38	257	34
Over 10 days	59	21	142	20
Total	279	100	741	100

TABLE IX.—SUTURE MATERIAL USED

	Series A		Series B	
	No.	Per cent	No.	Per cent
No. 000 black silk	124	44	304	40
Black silk plus buried suture (No. 80 or No. 120 cotton)	96	35	223	30
Stainless steel wire (.009 or .012)	45	16	90	12
No. 0000 black silk			81	11
No. 00 black silk			37	5
Other suture material	14	5	6	1
Total	279	100	741	100

facts. While 93 per cent of cases in series A were débrided in Korea a number required a second débridement after arrival in Japan. Furthermore, Table VI demonstrates that approximately 25 per cent more patients in the series A than in the series B group arrived in Japan during the 1 to 3 day period following injury, which enabled débridement and wet pressure dressing to be initiated at an earlier date and thus permitted earlier closure. The smaller number of débridements, therefore, was offset by the greater number of cases arriving in Japan at an earlier time after wounding.

Further, it is shown in Table VIII that 80 per cent of all cases were amenable to closure within the first 10 days after wounding. This

TABLE X.—TYPES OF CLOSURES

	Series A		Series B	
	No.	Per cent	No.	Per cent
Straight closure	148	54	596	80
Split graft	60	21	101	14
Graft and closure	38	13	31	4
Local flap	31	11	12	1.5
Distant flap	2	1	1	.5
Total	279	100	741	100

TABLE XI.—RESULTS

	Series A		Series B	
	No.	Per cent	No.	Per cent
Requiring no further surgery Healing per primam	198	71	467	63
Slight infection at suture line with no tissue loss	26	9	96	13
Loss of tissue 10% or less	27	10	30	4
Total	251	90	593	80
Requiring further surgery Loss of tissue 10–40%	17	6	45	6
Loss of tissue 50%	8	3	59	8
Loss of tissue from 60% to complete breakdown	3	1	44	6
Total	28	10	148	20

is an important figure in that the remaining 20 per cent are the problem cases that tax the ingenuity of the surgeon. These cases require such procedures as wound smears and cultures, repeated antibiotic sensitivity tests, more adequate débridement and removal of foreign bodies, and a complete review of the patient's physiologic state to determine any generalized cause for poor wound healing.

An analysis of Table IX reveals that heavy suture material is not necessary in delayed primary closure of war wounds. Between 70 to 80 per cent of cases may be closed by means of No. 000 black silk, with or without buried sutures of No. 80 or No. 120 cotton.

A greater percentage of grafts, grafts and closures, and local flaps were demonstrated in series A than in series B (Table X). A sum total of only 3 distant flaps were utilized in the entire series of 1,020 cases. This fact bears out the statement that except under certain specific conditions distant flaps have no role in the delayed primary closure program.

In series A, 90 per cent of the cases healed either per primam or had an insignificant loss of tissue so that no further surgery was required (Table XI). This result compares favorably with statistics compiled by Cleveland and Grove and Churchill in World War II. The 80 per cent result in series B does not compare as favorably. It is to be remembered that 9 medical officers, 2 of whom were not classified as surgeons, comprised the operators in this latter series. Of the remaining 7, 3 had previous experience with war wounds, 4 had none. The difference in results between the two series is statistically significant, and it is, therefore, tempting to conclude that the difference is due to variation in technique and clinical experience between the surgeons in the two series. There are so many variables in war wounds, however, that it is not believed that success or failure can be attributed to any one factor. It is believed, however, that better technique and greater clinical experience on the part of the surgeons will definitely increase the number of successful delayed primary closures.

Attention is called to the fact that no statistics have been presented on the number of days or weeks of hospitalization of individual patients. These figures were specifically not recorded as the author believes that they are of no value unless a complete and detailed description of the degree of muscle damage (as well as vascular and neural injury) in each individual case is likewise recorded. Furthermore, the voluntary effort of the patient in physical therapy and reconditioning influences the hospital stay to a significant degree. This would be difficult to evaluate and appraise in each case. It is interesting to note, however, that the average stay of all patients in this hospital during the reporting period was 53 days. Eighty-five per cent of these patients were on the surgical service, and of these surgical patients, 85 per cent had soft tissue injuries incurred in Korea. It is, therefore, logical to assume that the average patient with delayed primary closure required 50 to 55 days of hospitalization in this installation.

SUMMARY

A statistical analysis is presented of 1,020 consecutive Korean War wounds that were amenable to delayed primary closure. Eleven tables are presented which provide material of clinical value.

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OUTLET PELVIMETRY AND THE SYMPHYSIS-BIPARIETAL AND SACRAL-BIPARIETAL DIAMETERS

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IN our efforts to devise an acceptable method of pelvic evaluation, we must continue to assess various techniques. Although the entire pelvis must be investigated, one phase concerns the outlet pelvimetry. As part of a pelvic survey at this hospital, Thoms' modified outlet pelvimeter has been examined.

Recognizing the deficiencies of his original outlet pelvimeter, Thoms (2) reported a modification in 1946. Instead of measuring the anterior and posterior sagittal diameters of the outlet as defined by the level of the ischial tuberosities, this modified pelvimeter measures the distances to the lower edge of the symphysis and the sacral tip from the level at which a 9 centimeter transverse bar just passes through the pelvic arch. Since the average biparietal diameter approximates 9 centimeters, the anterior measurement is called the symphysis-biparietal diameter and the posterior measurement the sacral-biparietal diameter. The subsequent use of this modified outlet pelvimeter was reported in 1949 by Thoms and Cheney (3) and suggested the present study.

A series of 236 primiparous patients have been studied by clinical and roentgen pelvimetry. In the clinical study the Thoms' modified outlet pelvimeter was employed. The roentgen technique utilized was that of Thoms and Wilson (4). There was no particular system of patient selection. The incidence of pelvic types differs for this reason, but the series is large enough to permit comparison for the purposes to be considered.

For the purposes of this study, Thoms' system of pelvic classification has been adapted and modified to include both the inlet and midplane. The classification has been assigned according to the relative values of the anteroposterior and transverse diameters determined by roentgen pelvimetry. Classes 1, 2, 3, and 4 are identical with Thoms' platypellic, brachypellic, mesatipellic, and dolichopellic when applied to the inlet. The classes are:

Class 1. Transverse diameter is 3.0 or more centimeters greater than the anteroposterior diameter.

Class 2. Transverse diameter is 1 to 3 centimeters greater than the anteroposterior diameter.

Class 3. The transverse diameter is 0 to 1 centimeter greater than the anteroposterior diameter.

Class 4. The anteroposterior diameter is greater than the transverse diameter.

Class 5. The anteroposterior diameter is 0 to 1 centimeter greater than the transverse diameter.

Class 6. The anteroposterior diameter is 1 to 3 centimeters greater than the transverse diameter.

Class 7. The anteroposterior diameter is 3.0 or more centimeters greater than the transverse diameter.

Class 4 applies only to the inlet and classes 5, 6, and 7 apply only to the midplane.

In Table I, a comparison of the results of this study and that of Thoms and Cheney is given for the symphysis-biparietal and sacral-biparietal diameters in relation to the transverse diameter of the midplane and the class of inlet. Both studies indicate the narrowing of the midpelvis as the anteroposterior diameter relatively increases. Although not identical, the range of the outlet diameters is parallel.

Thoms and Cheney tabulated their data to indicate narrowing of the midplane proportionate to narrowing of the pubic rami that resulted in a larger symphysis-biparietal diameter. As is shown in Table II, we have not been able to demonstrate any such correlation. Even calculations to equilibrate the diameters according to an average pelvic capacity (not shown here) also failed to show a correlation.

In Table III, the relationship of the symphysis-biparietal and average midplane trans-

From the Department of Obstetrics and Gynecology, U.S. Naval Hospital, Chelsea, Mass. This study was authorized by the Bureau of Medicine and Surgery as Project NM 007 091.07 as one of the Clinical Studies at the U.S. Naval Hospital, Chelsea, Mass.

The opinions expressed are those of the author and do not necessarily reflect those of the Navy Department.

TABLE I.—AVERAGE SYMPHYSIS-BIPARIETAL, SACRAL-BIPARIETAL, AND TRANSVERSE MIDPLANE DIAMETERS FOR EACH CLASS OF PELVIC INLET

Class No.	Series*	No. cases	Average symphysis-biparietal diameter, cm.	Average sacral-biparietal diameter, cm.	Average midplane transverse diameter, cm.
1	T&C	0	5.6	6.4	11.6
	CNH	15			
2	T&C	45	4.9	7.6	11.0
	CNH	130	5.8	6.3	11.3
3	T&C	55	4.5	7.7	10.3
	CNH	75	5.7	6.7	10.9
4	T&C	45	5.0	8.0	9.9
	CNH	16	5.9	6.5	10.5

*T&C, Thoms and Cheney; CNH, U.S. Naval Hospital, Chelsea, Mass.

TABLE II.—AVERAGE MIDPLANE TRANSVERSE DIAMETERS FOR DIFFERENT SYMPHYSIS-BIPARIETAL DIAMETERS

Symphysis-biparietal diameter, cm.	No. of cases		Average midplane transverse diameter, cm.	
	T&C	CNH	T&C	CNH
2.5	3	0	11.1	—
3.0	10	1	11.0	11.0
3.5	2	1	10.8	11.6
4.0	28	13	10.4	11.7
4.5	12	12	10.6	10.8
5.0	58	57	10.6	11.2
5.5	15	48	10.4	10.6
6.0	13	57	10.5	11.1
6.5	1	16	9.9	11.1
7.0	4	29	9.5	10.9
7.5	0	5	—	11.5
8.0	0	5	—	11.6
9.0	0	1	—	10.5

TABLE III.—AVERAGE MIDPLANE TRANSVERSE DIAMETERS FOR DIFFERENT SYMPHYSIS-BIPARIETAL DIAMETERS FOR EACH CLASS OF PELVIC INLET

Symphysis-biparietal diameter, cm.	Transverse diameter, cm. Class of pelvic inlet			
	1	2	3	4
3.0		11.0		
3.5			11.6	
4.0	12.6	11.9	11.0	
4.5		10.9	10.9	9.0
5.0	11.4	11.2	11.3	10.7
5.5	12.2	11.2	10.6	9.9
6.0	10.9	10.8	11.0	10.2
6.5		11.7	10.5	10.8
7.0	11.9	11.1	10.9	9.3
7.5		11.5	11.6	11.5
8.0	11.1	11.9	11.1	
9.0			10.5	

TABLE IV.—AVERAGE MIDPLANE TRANSVERSE DIAMETERS FOR DIFFERENT TYPES OF INLET FOR EACH CLASS OF MIDPLANE

Inlet class No.	Transverse diameter, cm. Midplane class					
	1	2	3	5	6	7
1		12.2	12.5	11.7	10.3	
2		12.4	11.8	11.3	10.9	10.3
3	13.9	13.1		11.1	10.8	10.5
4				12.0	10.4	10.2

verse diameters is shown according to type of inlet. In Table IV, the average midplane transverse diameter is shown according to both the inlet class and midplane class. From Table III, the conclusion is that the variation in size of the midpelvis is a function of the type of pelvic inlet more than of the outlet diameter. This is shown more clearly in Table IV where the average midplane transverse diameter decreases as the anteroposterior diameter of the midplane relatively increases, but does not vary significantly according to the class of inlet. In Table V, the relation of the transverse midplane diameter to class of midplane is again shown and likewise shows lack of correlation with the outlet diameter.

In considering all of the data presented, consistent values are obtained only from roentgen pelvimetry. The varying clinical data demonstrate the results to be obtained from the use of any particular type of manual pelvimeter, if the obtaining of consistent numerical values by all examiners alike is made the goal. The comment is made that all data have either been obtained or checked by competent observers. Therefore, the conclusion is drawn that the symphysis-biparietal

TABLE V.—AVERAGE MIDPLANE TRANSVERSE DIAMETERS FOR DIFFERENT SYMPHYSIS-BIPARIETAL DIAMETERS

Symphysis-biparietal diameter, cm.	Transverse diameters, cm. Class of midplane					
	1	2	3	5	6	7
3.0					11.0	
3.5				11.6		
4.0			11.6	13.9	11.1	
4.5				11.2	10.6	
5.0		12.5	11.6	11.4	10.9	10.4
5.5			12.2	11.0	10.7	10.1
6.0	13.9		12.4	11.2	10.8	10.3
6.5			12.8	11.6	10.8	10.4
7.0		12.6	12.0	11.4	11.4	10.4
7.5					11.5	
8.0				11.6	11.6	
9.0					10.5	
Average	13.9	12.5	11.9	11.5	11.0	10.3
No. of patients	1	5	22	74	117	16

diameter alone has no significance as regards the midpelvis or inlet of a particular individual patient.

This experience has suggested that the place for clinical outlet pelvimetry lies in the sort of evaluation outlined by Moloy in which relative terms such as wide, average, and narrow are used to describe the outlet and its component parts. The use of a measuring device for absolute numerical values tempts the novice to seek a single denominator that will answer all clinical problems. It is suggested that the Thoms modified outlet pelvimeter may be useful in the hands of individual physicians. When employed in a relative descriptive sense, comparable to the use of the clenched fist, this pelvimeter indicates the available room beneath the pubic arch relative to the posterior segment.

Altogether, this study has indicated the need for a total pelvimetry which employs all clinical and roentgen techniques as aids in arriving at a clinical judgment. Roentgen techniques are needed to evaluate the inlet, midplane, sacral curve, and the relationship of the anterior and posterior segments. Clinical pelvimetry is required to evaluate the influence of the soft tissues, the elasticity of the perineum, and the mobility of the coccyx. Such total evaluation is gainfully pursued in labor and at delivery by means of lateral roentgenograms of the pelvis and sterile vaginal examinations. Such relative or descriptive pelvimetry is much more practical than the absolute pelvimetry of past teaching; it permits the weighing of factors other than the absolute size of the bony pelvis in the management of the individual obstetric patient.

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THE USE OF RADIOACTIVE COLLOIDAL GOLD IN THE TREATMENT OF SEROUS EFFUSIONS OF NEOPLASTIC ORIGIN

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INTRACAVITARY radioactive colloidal gold (Au^{198}) was first used for the treatment of peritoneal and pleural effusions due to carcinomatosis by Mueller in 1950. He showed that the introduction of this substance impeded the formation of serous effusions. Subsequently, reports by Smithers and King have appeared in the literature confirming Mueller's work. Since the number of cases thus far reported is small, and since this form of treatment appears to be a valuable contribution to the palliative management of the patient with widespread carcinoma, the authors wish to present their results in 19 patients.

PHYSICAL AND BIOLOGICAL CHARACTERISTICS OF AU^{198}

Radioactive gold emits a beta particle of 0.98 mev,[1] peak, and 2 gamma photons of 0.12 and 0.41 mev. Its half life is 2.7 days and thus it delivers approximately 75 per cent of its radiation in a period of 5.5 days. When administered intravenously in colloidal form, this isotope is deposited mainly in the reticuloendothelial system of the liver, and to a lesser extent in that of the spleen and bone marrow. When introduced into a serous cavity, it is deposited relatively rapidly and relatively uniformly over the serous surface. Being an inert colloid, most of the isotope remains fixed, and therefore little of it passes the membrane barrier to enter the general circulation during the radioactive life of gold.

TECHNIQUE OF TREATMENT

In the treatment of ascites due to peritoneal carcinomatosis, a paracentesis is performed in the usual manner. A small rubber catheter is then inserted through the trochar. The trochar is removed and the edges of the stab wound are tightly approximated about the catheter. This is done to prevent the escape of the radioactive material during its instillation. The catheter is then connected to an open burette containing approximately 250 cubic centimeters of sterile isotonic saline, and the system is tested for patency. If free flow is present, and no leaks are observed, 75 to 125 millicuries of radioactive colloidal gold are introduced into the burette, and the solution is allowed to flow rapidly into the peritoneal cavity.[1] The catheter is then removed and the wound is sutured tightly to prevent the escape of radioactive material. A collodion dressing is applied as an added precaution against leakage.

To insure a more uniform distribution of the radioactive material throughout the abdominal cavity, the patient is changed to a new and different position every 15 minutes for a period of 4 hours. The patient is then placed upon a radiation routine which involves minimal nursing care for a period consisting of 96 hours.

A similar procedure is followed for the intrapleural administration of radioactive colloidal gold except that the isotope is introduced through the thoracentesis needle. Because of the smaller cavity size, a dose of 35 to 75 millicuries is used. These patients also are changed in position periodically.

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[1]Mev, million electron volts.

[1]Because of the large doses of radioactive material used, protective measures to minimize the radiation hazard are carried out during the instillation. There are a number of satisfactory methods which may be used.

TABLE I.—GOOD RESULTS AFTER USE OF INTRAPERITONEAL RADIOACTIVE GOLD

Case Age, years Sex	Diagnosis	Frequency of paracenteses		Dose (Au^{198}) in mc.	Remarks
		Before Rx	After Rx		
1 50 F	Carcinoma of ovary	Once	None	100.0	Expired after 5 months
2 45 M	Malignant carcinoid	(1) 3–4 weeks	3 months	85.0	Received supervoltage Rx 5 months after 2nd dose
		(2)	None	120.0	
3 49 F	Carcinoma of ovary	Monthly	None	100.0	Expired in 6 months
4 64 F	Carcinoma of ovary	(1) Monthly	4 months	122.0	Expired 2 months after 2nd dose
		(2)	None	104.0	
5 72 F	Carcinoma of ovary	5–6 weeks	None	100.0	Expired 5 months
6 56 F	Carcinoma of ovary	(1) 2–3 weeks	2 months	105.0	Expired 2½ months after 4th Rx.
		(2)	6 months	100.0	
		(3)	6 months	104.0	
		(4)	2½ mo.	100.0	
7 58 F	Carcinoma of ovary	2–3 weeks	None	100.0	Expired 10 months

RESULTS

To date we have treated 19 patients with serous effusions of neoplastic origin. Of these, 13 were treated for ascites (Tables I and II) and 6 for pleural effusion (Table III). All of the patients had far advanced disease. Many of them had had previous courses of x-ray therapy. In all but 2 of the cases repeated withdrawals of fluid were required at weekly to monthly intervals prior to treatment.

Of the 13 patients treated with intraperitoneal gold, 7 showed a good response to therapy. These are summarized in Table I. In cases 1, 3, and 5 no further withdrawals of fluid were required until death 5 to 6 months after treatment. Three patients received more than 1 treatment (Cases 2, 4, and 6). Cases 6 and 7 are those in which the best results have been obtained. In Case 7 bimonthly paracentesis was required prior to treatment, but after a single instillation of radioactive colloidal gold, the patient remained free of fluid for 10 months, until her death.

Case 6 will serve as an example of the long term management of a patient with ascites. This patient, who had ovarian carcinomatosis, underwent paracentesis every 2 to 3 weeks prior to the first administration of radioactive colloidal gold. During a period of 15 months she received 4 treatments with the radioactive material. The first treatment delayed reaccumulation for 2 months, the second for 6 months, the third for 6 months, and the fourth for 2½ months, until death. Thus, a patient who would ordinarily require approximately 30 paracenteses in a period of 15 months has required but 4 as the result of radioactive colloidal gold therapy.

Table II lists the poor responses to intraperitoneal colloidal gold. It should be noted that 5 of these patients died within 1 month after treatment. This underscores the fact that the patients submitted for treatment usually had far advanced disease. Indeed, some of them were terminally ill and good results are not to be anticipated in such cases.

The results of intrapleural use of radioactive colloidal gold are in Table III. The response to therapy in this group was, in general, good. However, only 1 of these patients (Case 16) is still alive. Fluid accumulation was delayed for approximately 3 months in this patient, but at the present time he is requiring bimonthly thoracentesis. The patients in Cases 17, 18, and 19 were virtually moribund when submitted for treatment. Although no response to therapy was anticipated and although these patients died shortly after treatment, in each case there was definite inhibition of fluid formation.

Several side effects to treatment were noted. One was rapid formation of fluid after the introduction of radioactive material. This occurred in 2 patients but was not of serious consequence. Due to the rapid administration of the radiation, the problem of radiation sickness may arise. It is found that this may be controlled adequately by daily administrations of vitamin B complex preparations.

DISCUSSION

In the management of patients with widespread carcinomatosis, the control of serous effusions can assume major proportions. The use of irradiation is not a new concept in the treatment of these cases. External radiation has long been employed with some degree of

TABLE II.—POOR RESULTS AFTER USE OF INTRAPERITONEAL RADIOACTIVE GOLD

Case Age, years Sex	Diagnosis	Frequency of paracenteses		Dose (Au^{198}) in mc.	Remarks
		Before Rx	After Rx		
8 60 F	Carcinoma of cervix	Once	Once	25.0	Expired after 3 wks.
9 53 F	Carcinoma of ovary	2–3 weeks		100.0	Expired in 5 days
10 34 F	Meso-nephroma	Weekly	Weekly	100.0	Expired in 4 wks.
11 63 F	Carcinoma of ovary	2 weeks		100.0	Expired in 4 wks.; no paracentesis required
12 47 F	Carcinoma of breast	5–7 days	None	102.0	Expired 25 days
13 55 F	Carcinoma of stomach	Monthly	Monthly	100.0	Expired in 6 mo. without benefit

TABLE III.—RESULTS OF USE OF INTRATHORACIC GOLD (AU^{198}) IN 6 CASES

Case Age, years Sex	Diagnosis	Frequency of thoracenteses		Dose (Au^{198}) in mc.	Remarks
		Before Rx	After Rx		
14 49 F	Carcinoma of ovary	Once	Once	65.0	No further fluid accumulation; expired in 3 mos.
15 36 F	Carcinoma of ovary	(1) 2 weeks right (2) 3 weeks left	None None	50.0 50.0	No further fluid accumulation for 3 months, when patient expired
16 67 M	Metastatic carcinoma	3–4 weeks	None for 3 months	60.0	Good response for 3 mo. At present bimonthly thoracentesis
17 37 F	Reticulum cell sarcoma	Weekly	None	50.0	Expired in 6 weeks
18 75 F	Lympho-sarcoma	2–3 weeks	Once	50.0	Expired 25 days
19 61 F	Metastatic carcinoma	2 weeks	None	50.0	Expired 7 weeks

success. Radioactive colloidal gold is probably no more effective than external x-ray therapy for controlling the progress of the tumor in the peritoneal or pleural cavity. In fact, it may be less effective, since x-ray therapy possesses definite advantage in treating large tumor masses. However, for the control of serous effusions, Au^{198} appears to have several distinct advantages: (1) It can be administered in a single treatment and yet some prolongation of the radiation is obtained. (2) The radiation is confined primarily to the peritoneal or pleural surface with Au^{198}, whereas with external radiation no selective irradiation may be accomplished. (3) The tissues other than the serous membranes receive comparatively little radiation and, therefore, the radiation side effects are less than with x-ray for comparable doses to the serous membranes.

Although the exact mechanism of action of radioactive colloidal gold is not known, it is thought to be the effect of the radiation upon the minute tumor implants which stud the serous surfaces. The possibility that the reduction in the amount of effusion might be a direct effect upon the membranes themselves has been considered, but from some preliminary experiments this does not appear to be likely. Since most of the radiation delivered to the serous cavities arises from the beta particles emitted by the gold, the penetration is limited (on the average less than 1 mm.), and one would, therefore, anticipate a negligible effect upon large tumor masses. This has been borne out clinically.

An effort has been made to estimate the dose of radiation which has been delivered to the peritoneal cavity. For 100 millicuries introduced into the abdominal cavity, calculation indicates that about 2,000 rep[1] is administered.[2]

From our results, which are embodied in Tables I, II, and III, it can be seen that this form of treatment often will retard fluid formation of neoplastic origin. In our series, patients required the withdrawal of fluid at intervals of from 2 to 6 weeks prior to treatment; while after treatment, in those benefited, the interval was lengthened to from 2 to 6 months. Smithers, in a report of 60 cases

[1] A rep (roentgen equivalent physical) is that amount of radiation which produces an energy loss of 93 ergs/gram of tissue.

[2] In making the calculation, the average energy of the beta particle from Au^{198} has been assigned a value of 0.32 mev with an average penetration of 0.8 mm. in tissue. The peritoneal surface has been estimated to be 30,000 sq. cm. and it is assumed that the colloidal gold is uniformly distributed over this surface. The dose has then been averaged over the outer 0.8 mm. of the peritoneal surface. The gamma rays are considered to make only a negligible contribution to the dose.

treated in this manner, stated that over one-half had benefited symptomatically with absorption or cessation of formation of fluid. Andrews, in a series of 25 cases, obtained improvement in approximately two thirds of his patients. Our results, which show that approximately two thirds of the patients are benefited, are in accordance with the reports of these investigators.

In many of our patients, disease was far advanced and any beneficial effect of the treatment was looked upon with optimism. It must be borne in mind that intracavitary radioactive colloidal gold treatment is intended to have a palliative rather than a therapeutic effect upon the course of the patient's disease. There is no evidence that it prolongs life.

In 10 of the 19 patients the primary diagnosis was carcinoma of the ovary and it is in this group that results appear to be especially gratifying. Therefore, the question is raised as to whether radioactive colloidal gold should be used early in the treatment of carcinoma of the ovary in anticipation of metastatic spread to peritoneal cavity and subsequent effusion.

SUMMARY

Radioactive colloidal gold has been used in the treatment of 19 patients with serous effusion of neoplastic origin. Thirteen patients were treated for ascites and 6 for pleural effusion. Beneficial results were obtained in approximately two thirds of the patients. Effusion due to metastases from carcinoma of the ovary appeared to respond most favorably.

We believe that treatment with radioactive colloidal gold is a valuable adjunct to other forms of therapy in the palliative management of such patients.

There is no evidence that this treatment prolongs life.

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REFRIGERATION IN EXPERIMENTAL SURGERY OF THE AORTA

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EXPERIMENTAL reconstruction of the thoracic aorta has shown that hindquarter paralysis may follow temporary occlusion of the thoracic aorta. Carrel stated that occlusion of the thoracic aorta for more than 10 to 15 minutes usually caused paralysis of the hindquarters in the dog. Blalock and Parks found paralysis in nearly 50 per cent of their dogs who had occlusion of the thoracic aorta from 40 to 65 minutes. Hufnagel and Gross (15) found that 8 of 20 dogs were paralyzed when the thoracic aorta was clamped 10 to 50 minutes. One dog in 7 was paralyzed when the aorta was clamped 12 to 45 minutes after packing the back in ice. No mention of the rectal temperature was made in these experiments. Crafoord reported clamping the normal human thoracic aorta for as long as 27 minutes without paralysis in a case of patent ductus arteriosus. Blalock and co-workers reported paralysis in 1 of 4 human cases of coarctation treated with left subclavian artery anastomosis to the distal thoracic aorta. Beattie and co-workers reported 1 human patient with coarctation paralyzed after clamping the aorta and left subclavian artery for 38 minutes.

Carrel in 1910 recommended that if the aorta were clamped, blood flow could be maintained either by paraffined rubber tube shunts or by temporary intubation of the aorta. DeCamp and his associates and Hufnagel (14) have used tubes for intubation of the aorta during occlusion. Clatworthy and Varco used polyethylene shunts around the occluded aorta. In 19 dogs Clatworthy and Varco occluded the thoracic aorta for 60 or more minutes while employing polyethylene shunts. One dog died, 14 dogs survived, 4 dogs survived with stiffness of the hindlegs for less than 72 hours. Schafer and Hardin in clamping the canine thoracic aorta for 45 to 180 minutes found that 2 dogs died, 9 survived if polyethylene shunts were used.

Fay and Smith (10, 11, 19) studied refrigeration in the human patient with advanced cancer. Fay stated that he had lowered the body temperature of human patients to 75 degrees F. 100 times, and that he had maintained patients at 80 degrees F. for 7 to 10 days. He found that refrigeration caused a leucocytosis, no change in urinalysis, a slight fall in blood sugar and blood chloride, and shallow irregular respiration. Hook, Prec and associates, Talbott, and Wayburn have shown that cardiac irregularities, auricular fibrillation, bradycardia, alterations in electrocardiographic conduction time, prolonged electrical systole, and heart block are found at lowered body temperatures. Haterus and Maison showed that some dogs could survive body temperatures as low as 12 degrees C.

Penrod and Bigelow (3) showed in experimental animals that the oxygen consumption fell in proportion with the fall in body temperature. Bigelow and co-workers (2) excluded the heart from the circulation for 15 minutes in dogs at 20 degrees C. body temperature. Six of 39 dogs survived intact after this procedure. However, 19 of the 39 died with cardiac arrest or ventricular fibrillation during the operation. These authors reported that an artificial pacemaker in the form of periodic electrical stimulation of the sinoauricular node area of the heart successfully restored heart action in the cold state.

EXPERIMENTAL METHODS

Healthy mongrel dogs weighing 10 to 12 kilograms were used. Intravenous nembutal, 25 milligrams per kilogram body weight, was

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TABLE I.—AORTIC BLOOD PRESSURE

No refrigeration

Dog No.	Before occlusion	Immediately after occlusion		Immediately after unclamping	One minute after unclamping
		Proximal	Distal		
DF 766	136/90	200/160	71/70	83/42	132/66
DF 677	128/96	176/145	8/8	87/52	97/65
DG 834	120/96	184/144	40/40	104/64	—
DG 900	150/121	—	53/53	150/88	211/176

With refrigeration

Dog No.	Before occlusion	10–30 minutes after occlusion		Immediately after unclamping	One minute after unclamping
		Proximal	Distal		
DG 902	144/120	200/160	40/40	80/64	112/88
DG 904	157/113	200/130	35/35	90/50	90/50

used for anesthesia. The dogs to be refrigerated were placed in a bed of crushed ice covered with a plastic sheeting. The body temperature was recorded with a rectal thermometer. When the rectal temperature had fallen to values below 30 degrees C., the animal was removed from the ice and placed on an operating table. No further refrigeration was used.

In all the dogs studied, an intratracheal tube was inserted and positive pressure oxygenation of the lungs maintained with a Burns valve. With aseptic precautions the left thorax was entered and the thoracic aorta immediately distal to the left subclavian artery dissected free. The thoracic aorta at this location was occluded for varying periods of time by means of a Potts ductus clamp. After removal of the Potts clamp, the thorax was closed in a standard surgical fashion.

The refrigerated dogs were then placed in a water bath maintained at 40 to 45 degrees C. When the body temperature had risen above 35 degrees C. rectally, the dog was removed, dried, and wrapped in a blanket with hot water bottles. Intratracheal positive pressure oxygenation with the Burns valve was maintained in all except the first few refrigerated dogs until the rectal temperature was above 35 degrees C.

Pulse rate and respiration rate were recorded periodically in all dogs. The rectal temperature was recorded at intervals in all the dogs refrigerated. In several dogs aortic blood pressures were recorded by an electromanometer. The animals were observed for 2 weeks or more for evidence of hindquarter spastic paralysis or weakness.

RESULTS

Thirty-five dogs serve as the basis for this report. Ten animals had thoracic aorta occlusion for 60 minutes without refrigeration. It was found that the rectal temperatures of these animals during the occlusion varied from 35 to 39 degrees C. with the body temperature of 1 dog falling as low as 34 degrees C. for part of the experiment. Two animals had a spastic paralysis of the hindquarters and 2 animals exhibited persistent weakness of the hindquarters. Thus a 40 per cent incidence of spinal cord damage was found in clamping the thoracic aorta for 60 minutes.

Eighteen animals were refrigerated to have occlusion of the thoracic aorta for 60 minutes. Eight animals did not survive the experiments. Two animals were thought to die from an overdose of anesthetic agent, 1 animal at autopsy was found to have distemper, and 5 animals died from cardiac arrest or ventricular fibrillation. The temperature range of 25 degrees C. or lower was particularly prone to cause cardiac arrest. Of 10 animals that survived the experiments 1 animal exhibited questionably slight weakness of 1 hindleg. Thus a 0 to 10 per cent incidence of spinal cord damage was found when the thoracic aorta was clamped for 60 minutes at reduced body temperatures.

Seven animals were refrigerated to have the thoracic aorta occluded for 90 minutes. Two animals whose body temperature was lowered to 20 and 23 degrees C. respectively died from cardiac arrest. Five animals survived the experiments, and none of these animals showed any sign of hindleg paralysis. Thus a 0 per cent incidence of spinal cord damage was found when the thoracic aorta was clamped for 90 minutes at reduced body temperatures.

Aortic blood pressure measurements were taken in 4 dogs not refrigerated and 2 dogs refrigerated. After occluding the aorta of a nonrefrigerated dog, the aortic blood pressure proximal to clamp rose to 200/160, 176/145,

and 184/144 and distal to the clamp the blood pressure fell to 71/70, 8/8, 40/40, and 53/53. After occluding the aorta of the refrigerated dog, the aortic pressure proximal to the clamp rose to 200/160 and 200/130 and distal to the clamp the blood pressure fell to 40/40 and 35/35. These results are summarized in Table I.

The animal which exhibited the lowest aortic blood pressure distal to the clamp was a nonrefrigerated dog whose aortic pressure distal to the clamp fell to 8/8. This animal showed no signs of paralysis despite this low aortic pressure.

SUMMARY

Four of 10 dogs not refrigerated developed signs of hindquarter paralysis when the thoracic aorta was occluded for 60 minutes.

There was 1 questionable instance of weakness of 1 hindleg in 10 dogs refrigerated while the thoracic aorta was clamped for 60 minutes.

There was no instance of hindquarter paralysis when 5 dogs were refrigerated while the thoracic aorta was occluded for 90 minutes.

Ten additional dogs died during the refrigeration experiments. Seven of these 10 dogs died from cardiac arrest or ventricular fibrillation. Rectal temperatures below 25 degrees C. were particularly prone to cause cardiac arrest or ventricular fibrillation. Large doses of nembutal were poorly tolerated by the refrigerated dog.

CONCLUSIONS

Refrigeration will protect the spinal cord against temporary anoxia, but safer methods of refrigeration are needed.

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THE EFFECT OF EXPERIMENTALLY PRODUCED PANCREATITIS ON CANINE EXTERNAL PANCREATIC SECRETION

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CREDIT for being the first to produce pancreatitis by injecting bile into the pancreatic duct in 1856 has been given to Claude Bernard. Modern interest in the subject dates from the work of Opie which led to the theory that entrance of bile into the pancreatic ducts via the common channel often occurring at the ampulla of Vater might be the cause of some cases of pancreatitis occurring clinically.

Be this as it may, it is well known that forcible injection of bile into the pancreas of the dog uniformly produces pancreatitis, injections of 10 milliliters usually being fatal. If smaller quantities of bile are used, nonfatal pancreatitis of varying degrees of severity can be produced, according to Irenius. Many features of the resulting pathologic disturbances, including elevation of serum amylase and lipase, shock, edema, and necrosis of the pancreas and fat necrosis, simulate phenomena commonly encountered in pancreatitis in man.

The effect of this type of pancreatitis on external pancreatic secretion has not been previously studied, principally because a method had not been developed which would permit intraductal injection of bile and subsequent collection of pancreatic juice over a relatively long period. This requirement has been met in the present experiments, which were designed to study the course of nonlethal bile pancreatitis with regard to the pathologic changes in the pancreas and the associated disturbance of external pancreatic secretion.

METHODS

The studies were performed on 6 female mongrel dogs.

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Pancreatic juice was obtained by the method of Thomas and Crider as modified by Scott and his associates, in which a metal cannula placed permanently in the duodenum provides access to the papilla of the major pancreatic duct and permits one to cannulate it during experiments. With the animal under ether anesthesia the abdomen is opened and the minor pancreatic duct, which in the dog usually enters the duodenum with the common bile duct, is divided between ligatures. One end of the spool-shaped Thomas cannula is inserted into the lumen of the duodenum opposite the entrance of the major pancreatic duct, which enters the duodenum alone. The other end of the cannula is brought through a stab wound in the abdominal wall. Recovery from this procedure is rapid and the animals are usually ready for use after 2 weeks. Between tests the metal cannulas are capped and pancreatic juice enters the duodenum normally. Because there is no continuous loss of fluid and electrolytes from the gastrointestinal tract the dogs can be maintained in excellent condition indefinitely. During tests in which pancreatic juice is collected, the metal cannula is opened as the animal lies on one side and a fine olive-tipped tube is introduced transduodenally into the papilla of the major pancreatic duct. To prevent the loss of gastrointestinal contents other than pancreatic juice, the opening in the Thomas cannula is closed around the glass tube by a rubber diaphragm made from a finger cot (Fig. 1).

When the glass cannulas used for collecting pancreatic juice are properly fitted, leakage does not occur around them when juice is secreted at physiologic pressures. Injection of liquid such as bile into the ducts, however, requires higher pressures and under these circumstances leakage occurs if the standard

cannulas are used. To circumvent this difficulty a special cannula consisting of a glass tube with a bulb near its tip was devised to permit injection of bile transduodenally under pressures of 200 to 300 millimeters of mercury into the major pancreatic duct. When the tip of this cannula is placed into the duct the bulb can be pressed firmly enough against the papilla and the wall of the duodenum to prevent leakage of bile during forcible injection (Fig. 1, inset). The animals were anesthetized with pentobarbital sodium during injection of the bile. From 4 to 7 milliliters of bile obtained from the gallbladders of other dogs were used to produce nonfatal pancreatitis.

Two tests of external pancreatic secretion were employed. In the first, the juice secreted during 3 hours after ingestion of 200 grams of lightly cooked horse meat was collected for study; in the second, that secreted during 30 minutes after intravenous injections of Lilly's secretin was obtained. In all tests the volume of juice was recorded and aliquots were used for determination of content of bicarbonate by a titration method of Van Slyke and for determination of content of nitrogen by the Kjeldahl micromethod. The animals, which were fasted for 24 to 48 hours before tests, were easily trained to lie quietly while juice was being collected.

Several control tests were carried out before pancreatitis was produced and tests were conducted at intervals up to 24 weeks afterward to follow the course of the disturbance of external pancreatic secretion.

Plasma amylase activity was estimated by the ferricyanide method of Norby as modified by Lagerlöf without preliminary removal of protein. One milligram of maltose liberated from soluble starch in 15 minutes at a temperature of 37 degrees C. represents 1 unit of amylase activity.

Laparotomy was routinely performed 3 days after injection of bile to permit gross inspection and biopsy of the pancreas during the acute phase of the pancreatitis. Plasma amylase activity was followed during this period in 5 of the dogs. More complete study of the later effects of the bile pancreatitis on the glands was made during postmortem examinations at the conclusion of the study.

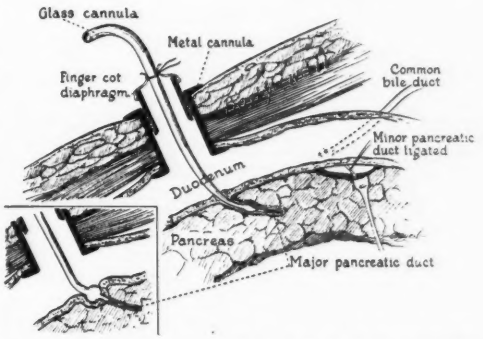

Fig. 1. Method employed for collection of pancreatic juice from the dog; inset, method of injecting bile into the major pancreatic duct.

RESULTS

General effects of injection of sublethal amounts of bile into the major pancreatic ducts of dogs. Because it was considered likely that injection of bile into the pancreatic ducts of dogs would be painful, the animals were anesthetized with pentobarbital sodium given intravenously when injections of bile were given. They recovered promptly from the anesthesia and in all instances, even those in which the pancreatitis proved to be most severe, appeared normal on the next day, ate food offered to them with evident appetite, and showed no sign of pain or discomfort. Plasma amylase values rose to a peak on the second and third days, often reaching levels twenty to thirty times the normal value of 10 to 20 units per cubic centimeter of plasma. No correlation was observed between the degree of rise in plasma amylase activity and the severity of the pancreatitis. All of the dogs survived laparotomy with inspection and biopsy of the pancreas on the third day after injection of bile. One dog appeared to be in good condition for 33 days after injection of bile though loss of weight from 13.0 to 11.5 kilograms occurred between the eleventh and twenty-eighth days. On the thirty-fourth day this animal refused to eat and on the following day it died. Necropsy failed to reveal the cause of death. No significant loss of weight occurred in the other 5 animals. All appeared in good condition when killed at from 78 to 183 days after injection of bile.

TABLE I.—DEGREE OF PANCREATITIS AND LATER PANCREATIC ATROPHY OBSERVED AMONG 6 DOGS FROM INJECTION OF BILE INTO THE PANCREATIC DUCT

Dog	Bile injected, ml.	Degree of acute pancreatitis		No. days to necropsy	Degree of atrophy at necropsy (per cent estimated)
		Gross	Microscopic		
1	4	Minimal	Minimal	61	Moderate (30)
	7	Moderate	Severe		
2	4	Minimal	Minimal	35	None
3	4	Moderate	Moderate	144	Severe (80)
	7	Moderate	Severe		
4	5	Severe	Moderate	101	None
5	4	Moderate	Severe	171	Moderate (50)
6	4	Severe	Severe	183	Severe (95)

Pathology. The acute phase of pancreatitis.—One acute experiment was performed on an anesthetized dog in which 4 milliliters of bile were injected into the major pancreatic duct transduodenally while the pancreas was under direct observation. The pancreas became bile stained and edematous within 20 minutes, and the "glassy" appearance noted by other observers developed. An additional 6 milliliters of bile produced no further immediate grossly observable change. Specimens taken for microscopic examination 50 minutes after the first injection of bile showed areas of complete necrosis of pancreatic tissue with a patchy distribution involving scattered segments of lobules. Illustrated in Figure 2, this observation emphasizes the fact that the areas of greatest immediate damage to the pancreas after bile is forcibly injected into the duct are unevenly distributed.

Information regarding a later stage in the acute phase of bile pancreatitis is based on gross observation of the pancreas at laparotomy performed 3 days after injection of bile and on microscopic examination of a biopsy specimen obtained at this time. Since 2 of the 6 dogs received bile twice, 8 observations of acute pancreatitis were made.

Gross changes varied from minimal edema to severe swelling and induration of the pancreas associated with widespread fat necrosis throughout the upper part of the abdomen.

For the purpose of describing gross appearance, the pancreatitis in glands approaching the normal in texture, appearing only slightly glassy and edematous and not associated with visible fat necrosis, is described as *minimal.* Pancreatitis associated with definite swelling, enlargement, and induration of the gland and with some fat necrosis in tissues near the gland is described as *moderate.* Pancreatitis characterized grossly by more marked swelling and induration of the gland accompanied by widespread inflammatory reaction throughout the upper part of the abdomen with edema and fat necrosis distributed widely is recorded as *severe.* Neither large hemorrhages into the pancreas nor hemorrhagic exudates in the abdominal cavity were encountered in these tests, probably because the doses of bile were purposely kept low enough to prevent death.

The microscopic appearance of biopsies of the pancreas 3 days after injection of bile likewise varied from that of nearly normal tissue (Fig. 3a) to a picture of severe damage (Figs. 3b and 4a). When the degree of pancreatitis was *minimal* the histologic structure of the acini and ducts was essentially normal, though some separation of groups of acini could be observed and was interpreted as indicating edema. Occasional areas of destruction of acini and proliferation of interstitial cells believed to be reticuloendothelial in origin were seen. In other instances in which the degree of pancreatitis as determined microscopically is described as *moderate,* the destruction of acinar tissue was more widespread, though still lobular in distribution, and was associated with infiltration with round cells and some polymorphonuclear leucocytes and with more intense proliferation of reticuloendothelial elements which frequently presented mitotic figures (Fig. 4b). When the destruction of pancreatic tissue was more generalized throughout the section with almost complete loss of normal architecture, the pancreatitis was described on microscopic grounds as *severe.* The distribution of the various degrees of acute pancreatitis which occurred is shown in Table I.

The state of the pancreas after recovery from the acute phase of pancreatitis.—At the time of necropsy from 35 to 183 days after the production of pancreatitis, no gross evidence of acute inflammation existed in or around the

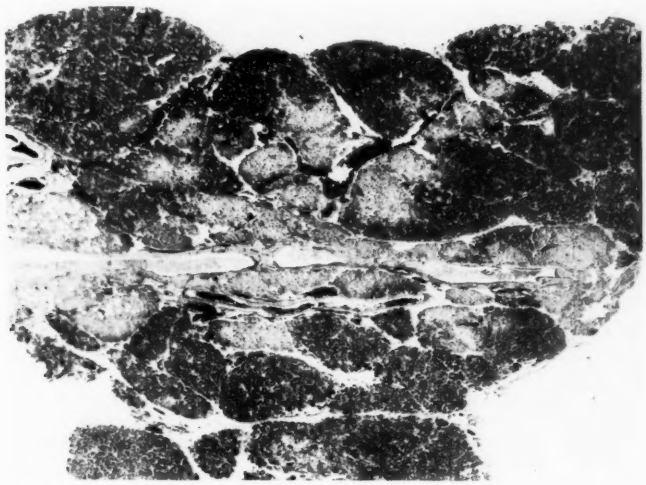

Fig. 2. Low power magnification (×13) of section of pancreas 50 minutes after injection of bile into pancreatic duct, showing the patchy distribution of the areas of immediate necrosis.

pancreas. The heart, lungs, liver, and the remainder of the gastrointestinal tract appeared normal. In 2 instances the pancreas appeared grossly and microscopically normal. In 1 of these (dog 2) almost no changes had developed 3 days after injection of bile. The other (dog 4) had shown severe gross changes and a moderate degree of microscopic pancreatitis at this earlier time. The recovery in this instance was remarkable. The remaining 4 animals showed varying degrees of pancreatic atrophy, most marked in the body of the gland nearest the entrance of the major pancreatic duct into the duodenum. It is in this region that the concentration of bile at the time of injection would be expected to be greatest. In the animal in which the most severe acute pancreatitis had developed (dog 6) the gland was found at necropsy 183 days later to consist of a thin cord of fibrous tissue with scattered groups of acini strung along the major duct. The major ducts in all 6 dogs were dissected free and opened at necropsy. They showed no evidence of obstruction or dilatation.

Microscopic study of these glands after the acute pancreatitis had subsided and reparative processes had taken place showed that areas which appeared normal grossly were essentially normal microscopically except for some increase in interlobular connective tissue (Fig. 4c). Individual acini were normal. Lobules of pancreatic tissue in regions where destruction had been extensive gave the appearance in microscopic sections of islands separated from each other by fibrous tissue (Fig. 4d). The final result was a loss of varying amounts of pancreatic tissue with repair involving fibrous replacement of the tissue which had been completely destroyed and perilobular fibrosis around the tissue which survived. The process of fibrous replacement of necrotic pancreas was evident in microscopic sections from 1 animal killed 61 days after induction of pancreatitis (Figs. 3c and d).

Changes in external pancreatic secretion after bile pancreatitis. In all instances an initial depression in pancreatic secretion occurred immediately after onset of pancreatitis. Some degree of recovery of function occurred with passage of time unless the damage to the pancreas was most severe.

In Tables II and III are presented values for volume of secretion, content and concentration of bicarbonate, and content and concentration of nitrogen in pancreatic juice secreted in response to secretin given intraven-

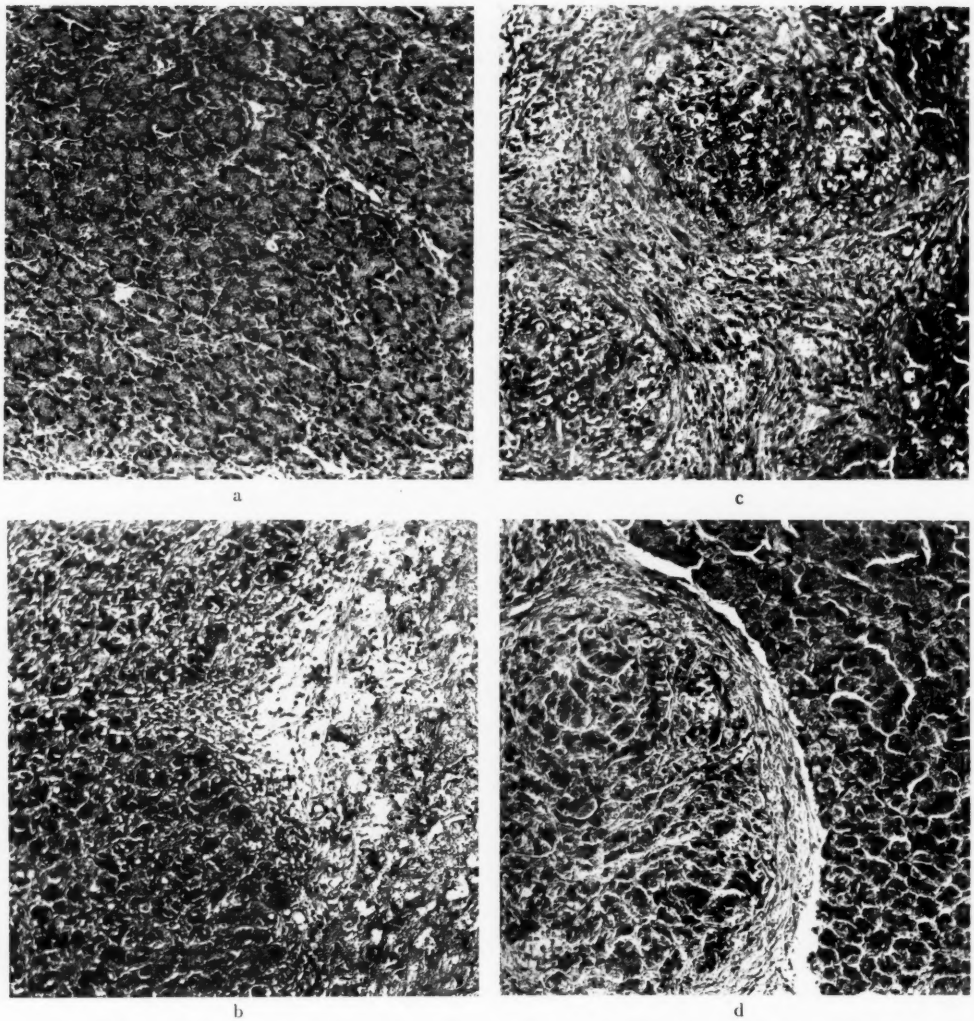

Fig. 3. Dog 1. a, Tail of pancreas (×115) 3 days after first injection of bile. Essentially normal. b, Body of pancreas (×115) 3 days after second injection of bile. Focal area of necrosis and edema. c, Uncinate process (×115) 61 days after second injection of bile. Necrotic acini undergoing fibrous tissue replacement. d, Body of pancreas (×115) 61 days after second injection of bile. Area of fairly normal acini near region undergoing fibrosis.

ously and to a meal of meat both before and at stated intervals after episodes of pancreatitis.

After an episode of minimal pancreatitis, dog 1 showed a mild suppression of pancreatic secretion during the first week but responded normally to a meal of meat during the second week and to an injection of secretin during the third week. After a subsequent injection of bile which produced moderate pancreatitis, the rate of secretion in response to both secretin and a meal was still reduced during the third week. The concentrations of bicarbonate and nitrogen in juice collected after feeding were

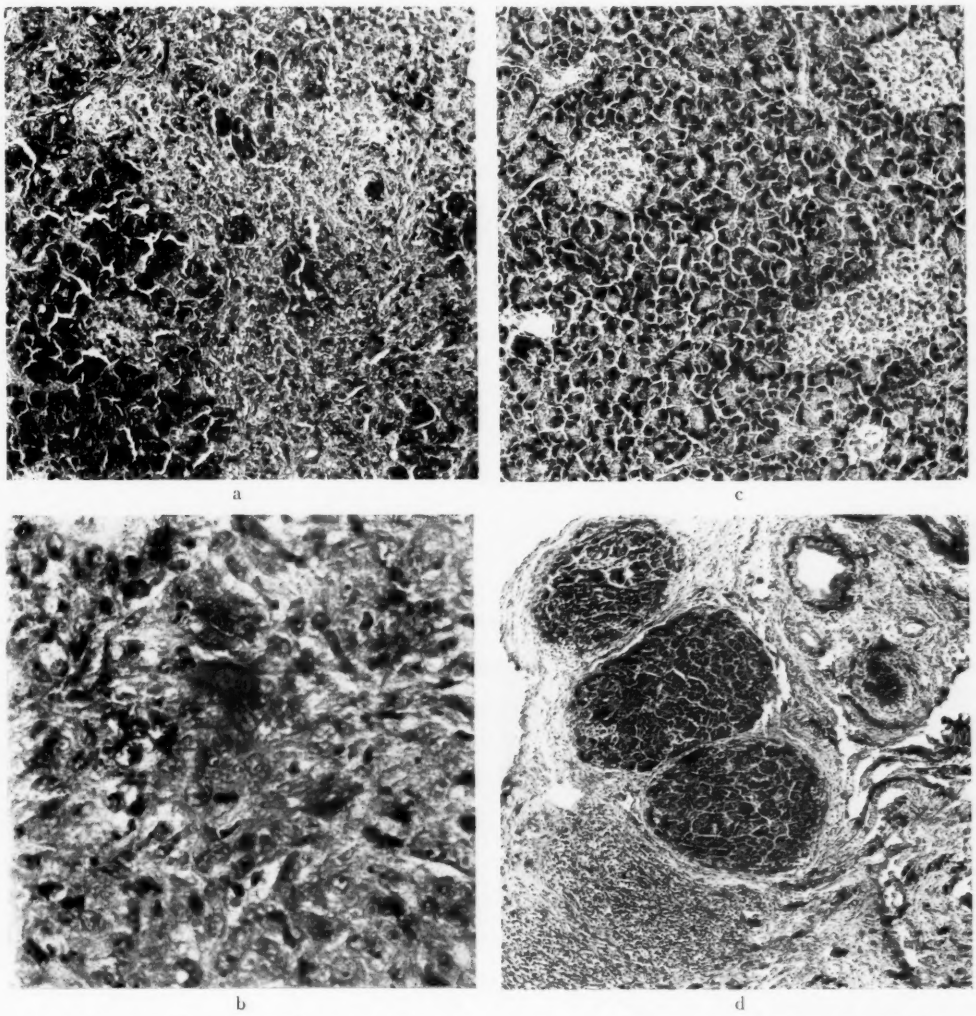

Fig. 4. Dog 6. a, Tail of pancreas (×115) 3 days after injection of bile. Severe acute pancreatitis with widespread destruction of pancreatic tissue. b, Same ×440. Note mitotic figure. c, Tail of pancreas (×115) after 183 days. Area of normal acini with many islets of Langerhans. d, Body of pancreas (×60) after 183 days. Areas of acinar tissue surrounded by fibrous tissue; atrophy and fibrous replacement of pancreas. A normal duct is visible.

normal. The studies had to be terminated because of difficulties with the metal cannula.

Dog 2, in which minimal pancreatitis developed with an early suppression of pancreatic secretion, had returned to nearly normal secretory responses to secretin and to feeding after 2 to 4 weeks. The animal died of undetermined cause 35 days after the injection of bile.

The third dog, like the first, was injected with bile on two occasions. Data are presented graphically in Figure 5. The first injection produced moderate pancreatitis followed by temporary diminution of the secretory re-

TABLE II.—EFFECT OF PANCREATITIS ON EXTERNAL PANCREATIC SECRETION IN DOGS 1, 2, AND 3

Dog and severity of acute pancreatitis	Time	Juice secreted during 30 minutes after I.V. injection of 15 units of secretin					Juice secreted during 3 hours after a meal of 200 gm. of horse meat				
		Vol., ml.	Bicarbonate		Nitrogen		Vol., ml.	Bicarbonate		Nitrogen	
			Total mEq.	mEq./l.	Total mgm.	mgm. per cent		Total mEq.	mEq./l.	Total mgm.	mgm. per cent
1	Before pancreatitis	9.0, 9.8	0.9, 1.0	104, 107	10.3, 3.9	114, 40	43.1–160.1	3.6–26.6	81–165	139–282	138–325
	Weeks after pancreatitis										
A Minimal	1	5.2	0.5	96	1.6	31	59.8	4.8	89	77	129
	2	—	—	—	—	—	76.2	8.2	108	151	198
	3	9.7	0.4	41	20	206	—	—	—	—	—
B Moderate	1	<0.1	—	—	—	—	63.9	4.1	64	63	99
	2	—	—	—	—	—	22.2	1.8	81	36	162
	3	3.0	0.2	67	2.0	67	27.1	2.5	92	69	255
2	Before pancreatitis	11.5, 18.3	1.8, 1.5	99, 133	13.4, 19.8	117, 108	84.7, 161.8	7.2–17.1	81–150	128–273	134–292
Minimal	Weeks after pancreatitis										
	1	2.0	0.2	100	0.6	30	46.8	3.4	73	75	160
	2	—	—	—	—	—	82.5	6.5	79	82	99
	4	7.7	0.8	104	14.0	182	—	—	—	—	—
3	Before pancreatitis	7.3, 10.3	1.3, 0.9	129, 123	25.2, 19.9	245, 273	49.8–77.7	3.3–5.7	66–73	151–234	255–315
	Weeks after pancreatitis										
A Moderate	1	3.5	0.3	86	2.8	80	57.0	4.2	74	131	230
	2	4.5	0.5	111	6.3	140	61.6	6.6	107	125	203
	5	8.9	0.6	67	15.0	169	—	—	—	—	—
B Severe	1	0.1	—	—	—	—	7.5	0.6	80	—	—
	2	—	—	—	—	—	21.2	1.7	80	57	264
	3	—	—	—	—	—	22.7	2.4	105.7	79	348
	4	2.1	0.2	95	5.4	257	—	—	—	—	—
	8	—	—	—	—	—	27.4	3.6	131	107	391
	19	3.2	0.3	94	5.0	156	34.9	4.2	120	88	252

sponse to secretin the following day and normal responses to a meal on the sixth and tenth days. The response to injection of secretin recovered more slowly. The second injection of bile produced severe pancreatitis with more marked initial suppression of pancreatic secretion. Though some recovery occurred, the rate of secretion after injection of secretin and after feeding remained approximately 35 and 50 per cent of control values even after 19 weeks. The concentration of bicarbonate and of nitrogen in the postprandial juice at this time was essentially normal (Table II). At necropsy the pancreas was estimated to be about 80 per cent atrophied.

Dog 4, with pancreatitis classified as moderate on microscopic examination and severe on gross examination, showed the usual great

TABLE III.—EFFECT OF PANCREATITIS ON EXTERNAL PANCREATIC SECRETION IN DOGS 4, 5, AND 6

Dog and severity of acute pancreatitis	Time	Juice secreted during 30 minutes after I.V. injection of 15 units of secretin					Juice secreted during 3 hours after a meal of 200 gm. of horse meat				
		Vol., ml.	Bicarbonate		Nitrogen		Vol., ml.	Bicarbonate		Nitrogen	
			Total mEq.	mEq./l.	Total mgm.	mgm. per cent		Total mEq.	mEq./l.	Total mgm.	mgm. per cent
4	Before pancreatitis	4.2, 7.3	0.8, 0.5	106, 112	20, 7.8	271, 187	82.2–131	6.9–13.6	70–130	153–213	117–227
	Weeks after pancreatitis										
	1	0.4	—	—	—	—	—	—	—	—	—
Moderate	2	—	—	—	—	—	66.7	8.3	113	208	360
	4	—	—	—	—	—	61.1	5.5	90	231	378
5	Before pancreatitis	8.7	0.9	103	10.3, 14.2	141, 142					
	Weeks after pancreatitis										
	1	0.6	—	—	0.9	150					
	3	1.2	0.06	50	0.1	—					
	5	2.5	0.2	82	—	—					
Severe	7	1.5	0.05	33	1.0	67					
	11	2.5	0.2	80	3.8	152					
	12	3.3	0.3	91	3.1	94					
	22	2.9	—	—	4.0	138					
6	Before pancreatitis	9.2	1.1, 1.2	122, 131	22.4, 17.9	246, 195	19.6–56.5	0.8–4.0	41–71	70–142	252–617
	Weeks after pancreatitis										
	1	0.4	—	—	0.8	200	2.8	0.1	36	2.5	89
	2	0.4	—	—	—	—	7.4	0.5	68	14.7	199
	4	—	—	—	—	—	4.7	0.3	64	5.4	115
Severe	8	0.5	—	—	—	—	3.0	0.3	100	5.2	174
	14	—	—	—	—	—	1.6	0.1	63	2.5	156
	22	—	—	—	—	—	2.7	—	—	3.6	134
	24	0.1	—	—	—	—	2.7	0.2	74	7.8	259

suppression of the response to secretin the day after injection of bile. Tests during the second and fourth weeks indicated that the animal produced about two-thirds the control volume of secretion in response to feeding and that the concentrations of bicarbonate and of nitrogen in this juice were normal. At necropsy, 101 days after onset of pancreatitis, the gland appeared to have been restored to normal. It is regrettable that further tests of secretion were not possible between the fifth and the fourteenth week after injection of bile, particularly because the absence of atrophy of the pancreas after 14 weeks was noteworthy.

The fifth and sixth dogs developed severe pancreatitis followed by prolonged suppression of pancreatic secretion for the duration of the study. Dog 5, in which only the response

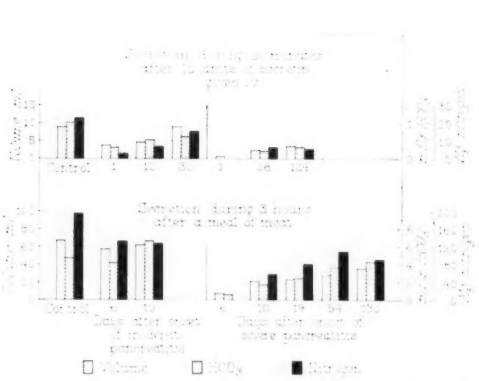

Fig. 5. Dog 3. Effect of moderate and severe experimental bile pancreatitis on external pancreatic secretion.

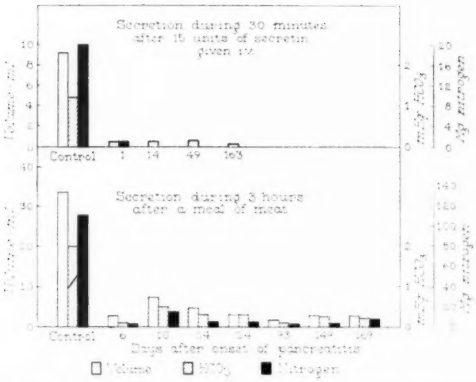
Secretion during 30 minutes after 15 units of secretin given I.V.
Secretion during 3 hours after a meal of meat
Control
Days after onset of pancreatitis
Volume
BHCO3
Nitrogen

Fig. 6. Dog 6. Effect of severe experimental bile pancreatitis on external pancreatic secretion.

to secretin was observed, improved for 5 weeks, after which the rate of secretion remained stable throughout a long period terminating in the last test 22 weeks after onset of pancreatitis. Necropsy revealed an estimated 50 per cent atrophy of the gland. Data from dog 6, which had the most severe acute pancreatitis and the greatest atrophy of the pancreas later, are shown graphically in Figure 6. Secretory responses both to secretin and to a meal were reduced to from 5 to 10 per cent of corresponding control values, and no improvement occurred over a period of 24 weeks. The pancreas was found to be 95 per cent atrophied.

Fat intake and output tests, performed by Dr. Richard B. Welbourn 4 weeks after the second injection of bile in dog 3 and after 10 weeks on dog 6, showed that 1.5 per cent and 3.7 per cent of ingested fat, respectively, were recovered in the feces. These figures are within normal limits and serve to emphasize the fact that great impairment of pancreatic function is compatible with normal absorption of fat in the dog.

The data indicate that though impairment of external pancreatic secretion is the rule during the acute phase of canine bile pancreatitis, the pancreas tends to recover its secretory ability, the ultimate degree of recovery depending on the extent of permanent damage to the pancreas. Even when the rate of secretion in response to the stimuli used remained low, the concentrations of bicarbonate and nitrogen in the juice were usually in the normal range, supporting the concept that the juice was qualitatively normal.

COMMENT

Many aspects of the pathology of pancreatitis as it is seen in man together with the consequent rise and fall of plasma amylase were simulated in the pancreatitis produced in these dogs. The same cannot be said of symptoms, however, and the apparent absence of signs of pain, of anorexia, and of lassitude in dogs known to have acute pancreatitis was striking. It is known, of course, that larger quantities of bile injected into the pancreatic ducts can produce shock and death associated with more severe hemorrhagic pancreatitis.

In all the animals, external pancreatic secretion was greatly depressed immediately after the pancreatitis was established, and some degree of recovery of secretory ability occurred thereafter. In general, the more severe the pancreatic damage, the less complete was recovery of the gland's ability to secrete. The juice secreted after recovery from acute pancreatitis was qualitatively normal with regard to appearance and content of bicarbonate and nitrogen, and the acinar cells remaining at this time presented a normal microscopic appearance. In the light of these observations, the following interpretation of the probable sequence of events is offered. Injection of bile

into the pancreatic duct in amounts used in this study resulted initially in widespread damage to the pancreas, some reversible and some irreversible. The great depression of external pancreatic secretion seen at this time could result from a combination of damage to acinar cells and edema with obstruction of fine ducts. If damage to the pancreas is minimal, complete structural and functional recovery is possible. If damage is more severe, part of the pancreatic tissue recovers whereas the part irreversibly damaged is absorbed and gradually replaced by fibrous tissue. The areas of atrophy and fibrous replacement tend to be spotty and unevenly distributed just as did the areas of immediate necrosis seen in the acute experiment depicted in Figure 2. Logically enough, the damage to the pancreas is more severe in portions of the gland near the site of injection of bile than in areas distant from this point. Since the main ductal system remains patent, the atrophy cannot be the result of closure of the larger ducts. After the pancreas has recovered from the acute phase of pancreatitis and the damage which was done has been repaired, there results a gland with less than the original mass of secretory acinar tissue. The ultimate capacity for external secretion depends upon the amount of functioning acinar tissue which remains.

SUMMARY AND CONCLUSIONS

1. A method has been presented by means of which external pancreatic secretion can be studied before and for long periods after damage to the pancreas has been produced by injection of bile into the pancreatic duct.

2. Degrees of sublethal pancreatitis varying from minimal edema to severe destruction of the gland with widespread fat necrosis were produced. Anatomic recovery following episodes of minimal and in 1 instance a moderate degree of pancreatitis was apparently complete. Severe degrees of acute pancreatitis were followed by varying amounts of atrophy of the gland with reduction in the mass of surviving acinar tissue.

3. The external pancreatic secretory responses to secretin and to a meal of meat were quantitatively greatly depressed immediately after onset of even minimal pancreatitis but tended to recover as time passed. The degree of recovery depended on the extent of damage to the pancreas, being prompt and essentially complete in instances of minimal pancreatitis which progressed to complete anatomic recovery and being very little in instances of severe pancreatitis which resulted in atrophy of the gland. Pancreatic juice secreted after recovery from pancreatitis was qualitatively normal with regard to concentration of bicarbonate and nitrogen.

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THE EFFECT OF INTRATHORACIC VAGAL STIMULATION ON THE ELECTROCARDIOGRAPHIC TRACING IN MAN

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DURING recent years, the authors have transected the homolateral vagus nerve immediately below the origin of the recurrent laryngeal as a palliative measure in a number of patients found to have an inoperable bronchogenic carcinoma at the time of exploratory thoracotomy. It was demonstrated that in the majority of patients pain and cough of bronchial origin are carried to the central nervous system by the homolateral vagus nerve (7, 12-14). A critical postoperative analysis of these patients has revealed that substantial alleviation of cough and deep chest pain is achieved without the occurrence of adverse sequellae (11). More recently bilateral vagotomy has been performed in patients with intractable asthma in an attempt to alleviate the pathologic physiology of this condition (6).

Definite concern existed during the initial performance of these procedures inasmuch as some cases of sudden death due to cardiac arrest coincident with vagal manipulation have been reported. Two such patients are cited from the earlier literature by Alvarez in which one died after a ligature was placed about one of the vagus nerves, and the other expired while a vagus nerve was being mobilized. Weeks and his associates reported the occurrence of cardiac arrest in a patient undergoing supradiaphragmatic vagotomy for peptic ulcer. Bradycardia was noted during the mobilization of the vagus nerves. Shortly after transection of one of the vagi, the anesthetist noted respiratory difficulties, an imperceptible pulse and absence of the heart beat. Moore and his associates reported a similar mishap in a patient 48 hours after transthoracic vagotomy. They thought the cause of death was due to anesthesia difficulties or due to a vagovagal reflex resulting in cardiac standstill. More recently Paine and Varco have reported the occurrence of cardiac irregularities in several patients and death in 2 patients undergoing surgery for pulmonic stenosis. Inasmuch as some of the arrhythmias were accompanied by slowing and dilatation of the heart, it was tentatively concluded that such were due to vagal reflexes initiated by operative trauma in the region of the hilus of the lung.

A review of the pertinent experimental literature reveals that it has long been appreciated that the regulation of the heart is due to a balanced action of the vagus and sympathetic nerves. The efferent fibers of the vagus are preganglionic in character and end in peripheral ganglia located in the auricle. Postganglionic fibers from these ganglia innervate the sinoauricular and auriculoventricular nodes, the auricular muscle, and the auriculoventricular bundle. Physiologically the vagus nerve maintains a persistent cardioinhibitory tone which may be demonstrated by bilateral vagotomy, the administration of appropriate drugs, or through inducing hyperactivity by direct vagal stimulation.

Bilateral transection of the vagus nerves results in tachycardia and a variable blood pressure response. Vagal stimulation produces a bradycardia, a weakening of the heart beat, a depression of cardiac conduction, and a reduction of the refractory period of auricular muscle. Electrocardiographic tracings obtained during vagal stimulation include the following changes: Prolongation of the PR and R-R intervals, sinus arrhythmia and bradycardia, sinoauricular block, changes in amplitude or inversion of the P wave, and a depressed or inverted T wave.

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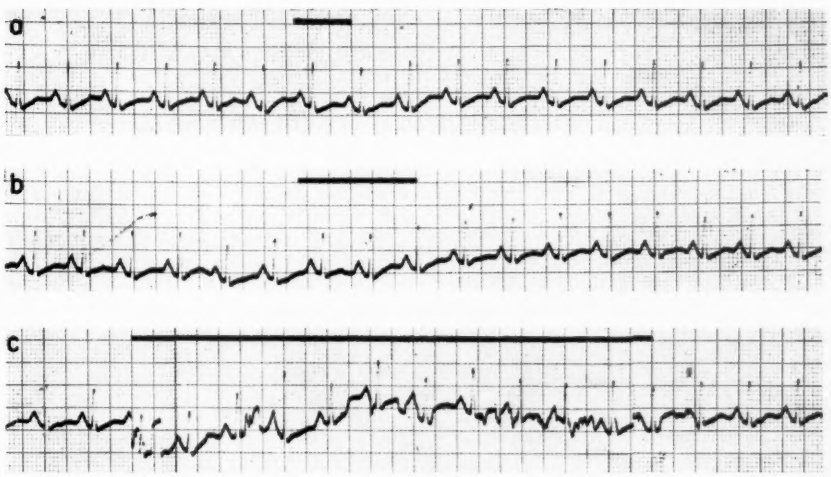

Fig. 1. Case 1. Electrocardiograms obtained during: a, pinching of the intact vagus nerve; b, transection of the vagus nerve; and, c, electric stimulation of the distal end of the divided vagus nerve. The black line immediately above each tracing represents the duration of vagal stimulation. With the exception of the distorted tracing confined to the period of electric stimulation, no changes secondary to vagus excitation are to be found. Note the regular occurrence of the QRS complexes during this period. The R-R intervals remain unchanged and of .44 second's duration throughout this series of tracings.

A few instances of deliberate stimulation of the vagus nerve in man are recorded. Weiss and Baker report the occurrence of bradycardia in 1 of 2 patients in whom the vagus nerve was pinched during surgery. Hill exposed and mechanically stimulated the exposed vagus nerve in 20 patients undergoing surgery for metastatic carcinoma or tuberculous adenitis of the cervical region. Although the general anesthesia and premedication employed possibly suppressed reflex activity to some degree, gentle pinching of the vagus nerve in 4 patients resulted in bradycardia, a decrease in amplitude or disappearance of the P wave, and extrasystoles. In addition he noted that these changes were characterized by a latent period, a slow development of maximal response, and long after-effects. McDowall assumed these latter phenomena to be characteristic of a reflex discharged centrally rather than due to direct vagal motor stimulation. Confirmation of this belief is afforded by the work of Iacobovici and his associates who found in 1 patient that stimulation of the distal end of the divided vagus was without effect, whereas stimulation of the proximal end resulted in bradycardia. All the aforementioned cardiac changes secondary to direct vagal stimulation are thought to represent true vagovagal reflexes in that both afferent and efferent members of the reflex arc are vagal in origin.

Frequent electrocardiographic studies have been reported concerning the cardiac effects of anesthesia, preoperative medication, and surgical manipulation. In many instances no constant or specific relationship could be established between the occurrence of arrhythmias and the type or depth of anesthesia or the steps in the surgical procedure. However, Maher and his associates have observed the occurrence of extrasystoles in 10 patients and bradycardia in 7 patients in apparent direct association with a visceral stimulation. Reid and Brace demonstrated the occurrence of extrasystoles, delayed conduction time, and bradycardia in patients under light general anesthesia in whom the tracheobronchial tree was stimulated by a catheter, McGill tubes, inflation of cuffs, spraying of the throat, and by the passage of bronchoscopes. These alterations in cardiac function occurred only during

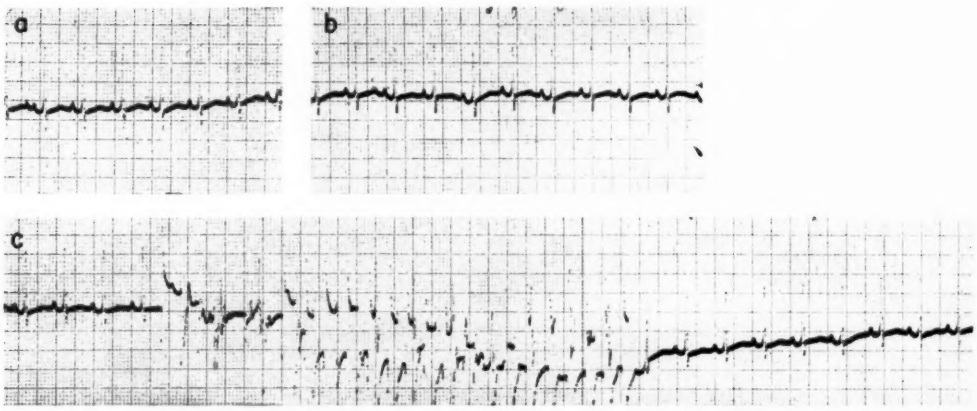

Fig. 2. Case 2. Electrocardiograms which were obtained during: a, incision; b, traction on the vagus nerve; and, c, electric stimulation of the intact vagus nerve. There are no changes in these tracings with the exception of electric interference during the brief period of electric stimulation.

mechanical irritation and were thought to be produced by vagovagal reflexes.

In recent years vagotomy has been performed frequently in the surgical treatment of peptic ulcer. The occurrence of cardiac standstill due to vagal manipulation in these cases is exceedingly rare. It appears that in the performance of this operative procedure, there is little danger of the occurrence of a vagovagal reflex leading to sequelae of a serious nature. The belief that manipulation of more proximal portions of the vagus nerve might give rise to a higher incidence of vagovagal reflexes has been expressed by Gullickson and associates. In our series of cases, vagotomy was performed immediately distal to the origin of the recurrent laryngeal nerve. It would appear that manipulation of the vagus nerve at this high point might give rise to a greater frequency of vagovagal reflexes. That such is not the case is evidenced by the following investigation.

ELECTROCARDIOGRAPHIC STUDY

This study is based upon the electrocardiographic findings in 30 patients who were found to have an inoperable bronchogenic carcinoma at the time of exploratory thoracotomy. As a palliative measure, the homolateral vagus nerve was transected just below the origin of the recurrent laryngeal nerve. The anesthetist prescribed the drugs of preoperative medication and employed the type of anesthetic that he considered indicated. The 30 patients were divided into two groups.

In the first group, consisting of 18 patients, electrocardiograms were obtained at the following intervals: (1) preoperatively, (2) during opening of the chest, (3) while traction was applied to the vagus nerve, (4) when the vagus nerve was crushed, (5) while transecting the vagus nerve, (6) during closure of the chest, (7) postoperatively.

Standard lead II was employed throughout the study. In addition the anesthetist watched for the occurrence of any cardiovascular or respiratory reflexes clinically discernible. With the exception of 1 patient in this first group, no changes were detected on the electrocardiograms. In this 1 patient the occurrence of cardiac arrhythmias was apparently directly related to the administration of cyclopropane anesthesia, since substitution of nitrous oxide-oxygen-ether was accompanied by return to normal rhythm.

Since the procedure described produced no clinical or electrocardiographic effects of vagal origin, electric stimulation of the vagus nerve was performed in the second group of 12 patients. In this group the intact vagus nerve, as well as the proximal and distal ends of the transected vagus nerve, were stimulated

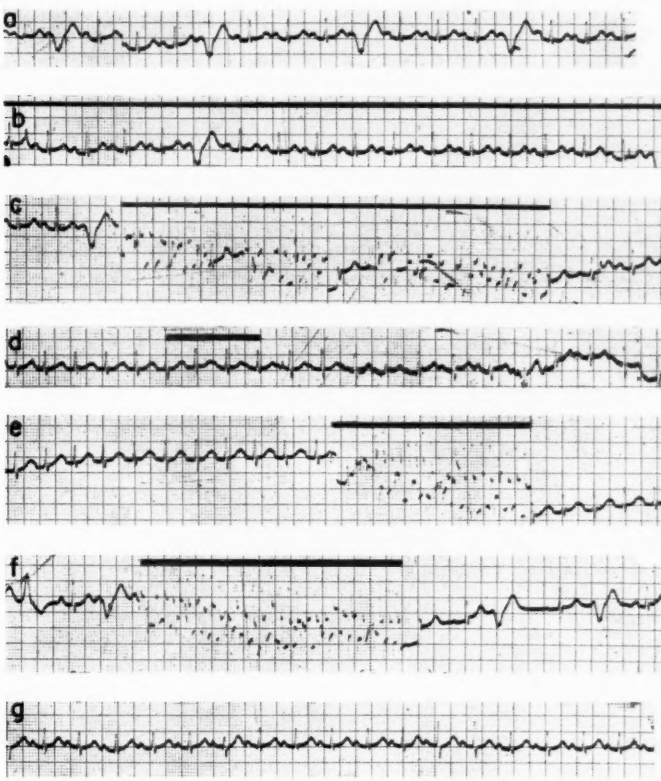

Fig. 3. Case 3. The black line indicates the duration of vagal stimulation. a, Note ventricular extrasystoles occurring every fourth beat while entering the chest. b, Traction on the vagus nerve produced no change in the tracing. c, The first 3 cycles following cessation of electric stimulation of the intact vagus nerve reveal changes due to increased vagal tone. Transient bradycardia, indicated by prolongation of the R-R interval, persists for 3 cycles. The subsequent 3 cycles reveal a decrease in the R-R interval probably representing an auricular tachycardia. d, After crushing the vagus nerve the R-R interval is slightly increased and the P wave becomes discernible, indicating a transition to sinus tachycardia. e, Electric stimulation of the central end of the divided vagus nerve produced no changes in the electrocardiographic pattern. f, After cessation of electric stimulation of the distal end of the divided vagus nerve, note the decrease in amplitude of the P wave and the prolongation of the PR and R-R intervals lasting 6 cycles. Note suppression of the sino-auricular node with beats arising from ectopic auricular and ventricular foci. g, Note absence of ventricular extra systoles during closure of the chest.

by an electric current produced by a 4.5 volt induction coil. The duration of this stimulation varied from 2 to 5 seconds. Prior to stimulating the vagus nerve, the efficiency of the induction coil and the adequacy of the current were tested by applying the electrode to the homolateral phrenic nerve. The resulting vigorous contraction of the diaphragm assured sufficient current. In this group, electrocardiograms were obtained at the following intervals: (1) preoperatively, (2) during opening of the chest, (3) while traction was applied to the vagus nerve, (4) during electric stimulation of the intact vagus nerve, (5) when the vagus nerve was crushed, (6) while transecting the vagus nerve, (7) during stimulation of the distal end of the divided vagus nerve, (8) during stimulation of the proximal end of the

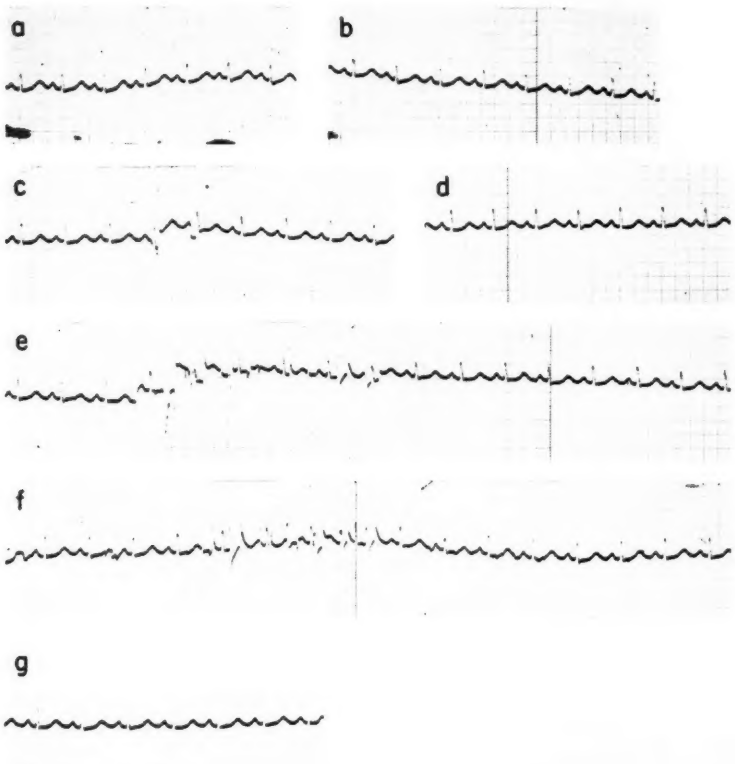

Fig. 4. Case 4. Electrocardiograms obtained during: a, incision; b, traction on the vagus nerve; c, electric stimulation of the phrenic nerve; d, crushing of the vagus; e and f, electric stimulation of the distal and proximal ends of the divided vagus nerve respectively; and, g, closure of the chest. No changes secondary to vagal stimulation were observed in this patient. Note the changes in the isoelectric level in c, during stimulation of the phrenic nerve. This is probably due to changes in the anatomic relationships of the heart secondary to vigorous unilateral diaphragmatic contraction.

divided vagus nerve, (9) during closure of the chest, (10) postoperatively.

Protocols of 6 patients so investigated, including the 2 in whom cardiac changes were noted, are herewith presented.

Case 1. No. 496466. J.M., a 54 year old male, was hospitalized with the diagnosis of bronchogenic carcinoma. On July 20, 1949, a right exploratory thoracotomy was performed. The premedication consisted of atropine 0.4 milligram and pantopon 10 milligrams. Anesthesia was induced with pentothal and curare and was maintained with cyclopropane and oxygen through an endotracheal tube. Electrocardiograms were obtained during the various phases of vagal manipulation and stimulation (Fig. 1). Other than the occurrence of a phenomenon, interpreted as interference in the third tracing, confined to the period of electric stimulation of the vagus, no changes are noted in the electrocardiographic pattern. The deflections above and below the isoelectric level probably represent the increased voltages produced by the rapid make and break of the circuit. It is of interest that the anesthetist was unable to perceive any change in the rate, rhythm, or volume of the pulse during this period.

Case 2. No. 492003-A. J.A., a 16 year old colored female, was subjected to right thoracotomy on November 9, 1949, under endotracheal nitrous oxide-oxygen-ether anesthesia. Premedication consisted of 100 milligrams of demerol and 0.4 milligram of scopolamine given 1 hour prior to surgery. The electrocardiograms obtained during various phases

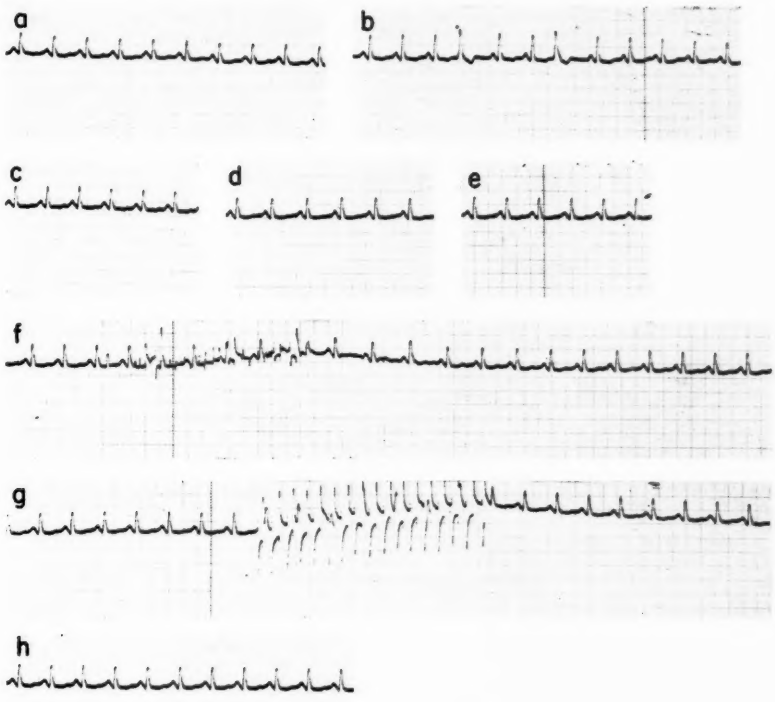

Fig. 5. Case 5. Electrocardiograms obtained during: a, incision; b, traction on the hilus of the left lung; c, release of hilar traction; d, crushing of the vagus; e, transection of the vagus; f and g, electric stimulation of the distal and proximal ends of the divided vagus nerve respectively; and, h, during closure of the chest. Note that premature ventricular systoles accompanied traction on the hilus of the left lung, b, and disappears when the traction was released, c. Inasmuch as such changes failed to occur secondary to direct vagal manipulation and stimulation they are probably not due to a vagovagal reflex, but secondary to changes in the anatomic relationships of the heart.

of the operative procedure are reproduced in Figure 2. With the exception of bizarre electrocardiographic phenomena interpreted as interferences, confined to the period of electric stimulation of the vagus nerve, no cardiac changes secondary to vagal stimulation were noted.

CASE 3. No. 500501-A. E.P., a 56 year old white male, was admitted to University Hospital on January 19, 1950, with a diagnosis of bronchogenic carcinoma. Premedication consisted of demerol 100 milligrams and scopolamine 0.4 milligram. With sodium pentothal-curare induction and endotracheal cyclopropane-oxygen anesthesia, a right exploratory thoracotomy was performed on January 21, 1950. Exploration revealed an inoperable tumor, and a palliative vagotomy was performed just below the recurrent laryngeal nerve. The electrocardiograms obtained during the operative procedure reveal significant changes secondary to vagal stimulation. These changes lasting 3 to 6 cycles, include a decrease in amplitude of the P wave, an increase in the PR and R-R intervals (bradycardia), auricular tachycardia, sinus tachycardia, and suppression of the sinoauricular node with beats arising from ectopic auricular and ventricular foci (Fig. 3).

CASE 4. No. 500076. B.S., a 53 year old white female, was subjected to left exploratory thoracotomy on January 5, 1950. Premedication consisted of morphine 15 milligrams and atropine 0.4 milligram. Anesthesia was induced with pentothal and curare and was maintained with endotracheal cyclopropane and oxygen. No changes were noted on the electro-

Fig. 6. Case 6. Electrocardiograms obtained during: a, surgical anesthesia; b, incision; c, traction on the vagus; d and e, electric stimulation of the intact vagus nerve; f, transection of the vagus nerve; g and h, electric stimulation of the distal and proximal ends of the divided vagus nerve; and, i, closure of the chest. Obvious electrocardiographic changes secondary to increased vagal tone are noted in tracings, d, e, and h. These consist of a decrease in amplitude, inversion, and absence of the P wave, prolongation of the PR and R-R intervals, ventricular extrasystoles and a generalized decrease in amplitude of all complexes in tracing e. These findings, although transient and lasting only 8 cycles, represent a bradycardia and a suppression of the sinoauricular node with beats arising from ectopic foci.

cardiographic tracings obtained during various phases of vagal manipulation and stimulation (Fig. 4).

Case 5. No. 501308-A. R.B., a 50 year old white male, was subjected to left exploratory thoracotomy on March 3, 1950. Demerol 100 milligrams and atropine 0.4 milligram were given 1 hour preoperatively. After sodium pentothal-curare induction, endotracheal cyclopropane-oxygen anesthesia was administered. It is of interest that traction on the hilus of the lung was associated with premature ventricular systoles, whereas direct vagal stimulation resulted in no electrocardiographic changes (Fig. 5).

Case 6. No. 501607-A. R.F., a 47 year old white female, was subjected to right exploratory thoracotomy on March 1, 1950. Demerol 100 milligrams and scopolamine 0.4 milligram were given 1 hour preoperatively. Anesthesia was induced with sodium pentothal-curare and was maintained with endotracheal nitrous oxide-oxygen and pentothal. Significant cardiac changes secondary to vagal stimulation were not only noted on the electrocardiographic tracings but were also noted clinically by the anesthetist (Fig. 6). The electrocardiographic changes lasting 4 to 8 cycles include a decrease in the amplitude

or inversion of the P waves, disappearance of the P wave, ventricular extrasystoles, prolongation of the R-R interval, and suppression of the sinoauricular node with beats arising from ectopic foci (auricular, nodal, and ventricular).

DISCUSSION

In the first 18 patients studied no cardiac derangements related to vagus nerve manipulation were discernible. In this group 1 patient presented cardiac arrhythmias which apparently were related to cyclopropane anesthesia, since substitution of nitrous oxide-oxygen anesthesia was accompanied by a return to normal rhythm. It is well known that the administration of cyclopropane anesthesia is frequently attended by cardiac arrhythmias.

In the second group of patients, in which electric stimulation of the vagus nerve was performed, only 2 patients showed electrocardiographic evidence of cardiac changes secondary to vagal stimulation. These transient changes lasting from 2 to 8 cycles consisted of prolongation of the PR and R-R intervals (bradycardia), a decrease in the amplitude or inversion of the P wave, disappearance of the P wave, auricular tachycardia, sinus tachycardia, and suppression of the sinoauricular node with beats arising from ectopic foci (auricular, nodal, and ventricular). The relative infrequency of these transient changes produced by stimulation of the vagus nerve in man is difficult to reconcile with the incidence found in the experimental literature.

A possible explanation of this discrepancy may be that the threshold of vagal cardioinhibition in man is higher than in the species studied experimentally. It is conceivable, also, that the electric current employed in this investigation was of insufficient voltage to overcome the threshold of vagal cardioinhibition in the majority of patients. It would appear, however, that a current capable of producing a vigorous diaphragmatic contraction when applied to the corresponding phrenic nerve, should be sufficient to bring about cardioinhibition when applied to the vagus nerve.

Other factors to be considered are the drugs administered as premedication and the type of anesthesia employed. Numerous drugs have been demonstrated to affect cardiac function through their influence on vagal tone. Vagal cardioinhibition is accomplished by the liberation of acetylcholine at the postganglionic nerve endings. Atropine, scopolamine, some barbiturates, and curare are anticholinergic drugs, and reduce or abolish the effect of vagal stimulation. The doses usually employed clinically, however, are ineffective in achieving complete vagal paralysis. All of the patients in our series received at least 1 and sometimes 3 of these anticholinergic drugs, either in the form of preoperative medication or during the induction of anesthesia. In this way some protection against the occurrence of vagovagal reflexes was afforded in our series of cases. Intrathoracic operative procedures are often time-consuming and metabolic breakdown of the drugs with subsequent diminution of their protective action probably occurred prior to conclusion of the investigative procedures.

These findings suggest that, in patients under satisfactory anesthesia, the occurrence of cardiac irregularities and cardiac arrest, as a result of a vagovagal reflex, is less common than has been previously supposed.

That anoxia is probably the most important factor in the pathogenesis of this condition is suggested by concomitant observations on other patients, in whom cardiac irregularities and cardiac arrest occurred during intrathoracic procedures. On several occasions gross cardiac irregularities have occurred in association with respiratory difficulties. Return to normal rhythm has taken place when good oxygenation was established. The experimental literature substantiates this belief. Greene and Gilbert in studying the late cardiac effects of anoxemia in man, gradually lowered the oxygen tension of inspired air to 5 to 10 per cent over a period of 20 to 30 minutes. They noted the following changes: progressive suppression of the sinoauricular rhythm, establishment of auriculoventricular rhythm with its characteristic slow and regular beat, decrease in conduction in the internodal region, and reversed rhythm and reversed internodal conduction. Rapid recovery from all these disturbances occurred within seconds after the individual was allowed to breath fresh air.

SUMMARY

1. The cardiac effects of intrathoracic vagal manipulation and stimulation were studied in 30 patients by means of electrocardiograms. In the last 12 patients investigated, the intact vagus nerve and the proximal and distal portions of the divided vagus were electrically stimulated.

2. Only 2 patients gave evidence of cardiac changes due to vagal stimulation. These changes were transient, lasting 2 to 8 cycles, and were of a minor nature.

3. The relative infrequency of cardiac changes secondary to vagal stimulation suggests that in patients under satisfactory anesthesia, cardiac arrest due to vagovagal reflex is less common than has been previously supposed.

4. Observations of other patients, in whom cardiac irregularities and cardiac arrest occurred during intrathoracic procedures, suggest that anoxia is probably the most important factor in the pathogenesis of such cardiac derangement.

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SURGICAL TREATMENT OF THE ARTHRITIC HIP

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THE purpose of this study is not to advocate any one type of surgery for the painful osteoarthritic hip but rather to form an unbiased evaluation of the various types of operation now at our disposal—arthrodesis, Smith-Petersen mold arthroplasty, and prosthetic replacement type arthroplasty. In this review an attempt has been made to set forth definite indications and contraindications for each of the currently used procedures at the New York Orthopaedic Hospital. The three different methods will be discussed separately.

ARTHRODESIS

Arthrodesis was performed on 128 patients for osteoarthritis of the hip. The follow-up period ranged from 2 to 13 years. The chief indication for this surgery was pain. All patients obtaining a solid fusion had no pain in the hip joint. Figure 1 shows a preoperative roentgenogram of a patient with arthritis of the hip in which an arthrodesis was to be performed. Figure 2 is a follow-up film taken 1 year later showing solid arthrodesis. Nine per cent of the patients developed some pain in the knee postoperatively and 33 per cent complained of back pain, although 11 per cent had some back pain prior to the operation. Seventeen per cent failed to obtain a solid arthrodesis on the first attempt. Figure 3 shows a preoperative film of a hip in which arthrodesis was attempted. Figure 4 shows a pseudarthrosis of the same case. It would seem that the reason a pseudarthrosis developed was that the principle of intra-articular fusion, plus internal fixation, plus bone graft was not adhered to at the time of surgery. Fifty per cent of the cases with pseudarthrosis became solid following a second arthrodesing operation. The severity of the limp decreased markedly and all patients could walk greater distances following a solid arthrodesis. This study indicates that the younger age group obtain the best results both as to function, rapidity of union, and a lower pseudarthrosis rate.

Indications. In summarizing the long term follow-up studies, arthrodesis of the hip joint is indicated in: (1) The younger age group because such a person can adapt more easily to an immobile hip joint. (2) Unilateral hip involvement which permits fusion because a normal opposite hip and a mobile lumbar spine will substitute to a great extent for motion lost in the arthrodesed hip. (3) The manual laborer who has the security of a more stable hip which can withstand stress and strain better than the average arthroplasty. (4) The unco-operative type of patient who expects surgery, and surgery alone, to produce a normal hip and who would not co-operate in the necessary postoperative exercises following arthroplasty. These patients progress much better with an arthrodesis. (5) Destruction of the hip joint due to previous sepsis since the possibility of a flare-up of latent infection is less likely in fusion. Should it occur, however, the result is not nearly as compromising as it is in an arthroplasty.

Contraindications. Arthrodesis is contraindicated in: (1) The older age group because arthrodesis is a more shocking operation than arthroplasty. (2) Bilateral hip involvement since two arthrodesed hips are extremely disabling and the surgeon is generally reluctant to perform a hip fusion with possible necessity of surgical intervention on the opposite side. It is true that an arthrodesis may be performed on one side, an arthroplasty on the other, but the fact that the arthroplasty might not be sufficiently successful makes this plan hazardous. (3) Sedentary occupations since these patients require less stability than does a manual laborer and are likely to place a high value on mobility as an aid in sitting. (4) Low back anomalies or osteoarthritis of the lumbar spine frequently cause limited motion and loss of the compensatory factor. Because of this the patient has difficulty bending

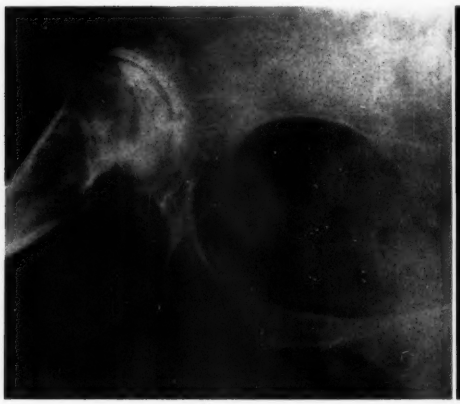

Fig. 1.

Fig. 2.

Fig. 1. Preoperative x-ray of patient with arthritis of the hip which was arthrodesed.
Fig. 2. Follow-up film 1 year later showing solid arthrodesis.

or sitting and is prone to low back pain which may be disabling.

Older patients cannot be immobilized for the necessary months required for fusion. It must be realized that there is a definite pseudarthrosis rate attendant with all fusion operations of the hip joint. Such a procedure must be seriously considered before subjecting a patient to prolonged immobilization.

SMITH-PETERSEN MOLD ARTHROPLASTY

Sixty-three Smith-Petersen mold arthroplasties for osteoarthritis of the hip have been performed. Seventy-five per cent had bilateral disease, the remainder were unilateral. In the majority of these cases the possibility of the necessity for eventual surgery on the opposite hip joint was great. The follow-up period ranged from 1 to 12 years with an average of 5 years. The patients valued the relief of pain more than the increase in motion. No correlation was found between pain and degree of motion. A limp persisted in all cases.

Indications. Mold arthroplasties are indicated in: (1) The middle age group since these

Fig. 3.

Fig. 4.

Fig. 3. Preoperative film of a hip in which arthrodesis was attempted.
Fig. 4. Pseudarthrosis of the same case as in Figure 3.

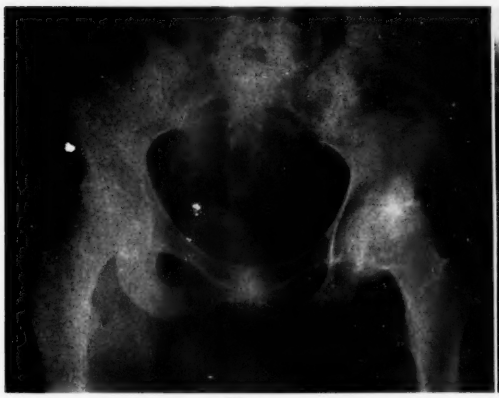

Fig. 5.

Fig. 6.

Fig. 5. Distribution of osteoarthritis before mold arthroplasty.
Fig. 6. Five year follow-up film. The end result, as recorded by Judet method of evaluation, was amelioration rate of 10.

patients are usually conscientious in their exercise routine and consequently receive the most satisfactory improvement in motion. (2) Bilateral hip involvement in which cases arthrodesis of the involved hip would be unwise because of the possibility of future trouble in the opposite hip. (3) Sedentary occupations as these patients value motion more than stability. (4) The co-operative patient since co-operation is of the utmost importance. It was found that the arthroplasty will be successful only if the patient is a conscientious, hard working individual who is determined to do his exercises religiously. (5) The coxa valga type of hip in which the anatomic acetabulo-femoral head relationship can best be reconstructed by having a mechanical device loose not only in the acetabulum but also on the head. (6) The shallow acetabulum. If a new acetabulum has to be formed the mechanical relationship can best be reconstructed by a vitallium mold. A replacement prosthesis is more adaptable when no change in the contour of the acetabulum is required.

Conservation of "working stock" has been emphasized by Smith-Petersen as being extremely important. Should further surgery be required on a hip which has been subjected to a mold arthroplasty this can be done with relative ease since sufficient bone remains for other reconstructive procedures or fusion. Figure 5 shows distribution of osteoarthritis before a mold arthroplasty was performed. Figure 6 shows a 5 year follow-up film. The end result, as recorded by the Judet method of evaluation, was amelioration rate of 10.

Contraindications. Mold arthroplasties are contraindicated in: (1) The old age group in which patients the prosthetic replacement type of operation may be more desirable when life expectancy is short. (2) Manual laborers because the hip is not as stable as in arthrod-

Fig. 7. Complication of bony encapsulation of the mold in which the amelioration rate as recorded by Judet standards was 2.

Fig. 8. Film of patient with an Austin Moore vitallium prosthesis.

esis. (3) The unco-operative patient who will not work hard on his exercises to develop his hip joint musculature and to preserve the range of joint motion. (4) Disintegration of the femoral head which is usually due to avascular necrosis but may also be caused by malposition from an old slipped epiphysis or fracture. Because of the deformed femoral head it is often impossible to reconstruct the head sufficiently to give adequate support to the mold. (5) Obesity since an obese patient is unwilling to co-operate in a weight reduction regimen prior to surgery it is felt that he lacks sufficient stamina to co-operate in his exercises postoperatively.

Unusual circumstances, such as poliomyelitis, muscular dystrophy, myositis ossificans, and previous failure of arthroplasty due to encapsulation of the mold by bone may be contraindications in the individual case. Figure 7 shows a complication of bony encapsulation of the mold in which the amelioration rate, as recorded by Judet standards, was 2.

While the following are not specific contraindications to mold arthroplasty they are important factors to be considered: (a) A mold arthroplasty is technically a more difficult operation than the usual prosthetic replacement type of arthroplasty. (b) Convalescence following a mold arthroplasty is longer than after the replacement type. (c) A final result in motion in the mold arthroplasties was found to be less than that obtained with the replacement type of prosthesis. Long term follow-up studies may alter this opinion.

PROSTHETIC REPLACEMENT TYPE ARTHROPLASTY

The third method of treatment of the painful arthritic hip is the femoral head prosthetic replacement arthroplasty. During the past

Fig. 9.

Fig. 10.

Fig. 9. Preoperative film of a patient in whom an arthroplasty of the Judet type was performed.
Fig. 10. Follow-up film at the end of 1 year. In this case the amelioration rate was 10.

24 months 36 Judet type arthroplasties, 3 Austin Moore, and 2 Thompson vitallium prosthesis type arthroplasties for osteoarthritis of the hip have been performed. In these the average age was 61 years. The follow-up period is much too short to evaluate long term results. Judet has recently reported his follow-up study on 620 cases varying from 5 months to 5 years. He rated 64 per cent as good or excellent results. This corresponds very closely with the results reported in a series of Smith-Petersen mold arthroplasties as reported by Wilson. In the present study, which covers a 7 year period, it was found that motion gradually decreased in the mold type arthroplasties even though it was increased immediately postoperatively. In the prosthetic replacement arthroplasties it was found that there resulted a greater range of motion immediately after operation and for the follow-up period of 2 years. However, long term results remain indefinite. Convalescence appears easier in the prosthetic type procedure than in the mold arthroplasty and ambulation and weight bearing can be instituted earlier. The patient's return to work is also accelerated. Twenty-seven cases were analyzed at the end of 1 year. At that time all replacements were tight and none showed femoral neck absorption or disintegration. Two patients had developed bursitis in the greater trochanteric area and required local treatment. Only 2 patients showed no improvement in range of motion and both of these had previously undergone other arthroplasty procedures.

Indications. In summary a prosthetic replacement type arthroplasty is indicated in: (1) Old age since this procedure permits early ambulation and more rapid return of motion. The factors favoring this procedure in the elderly patient are: technically an easier operation, shorter operating time, more rapid rehabilitation, greater immediate motion, less operative shock, and shorter hospitalization. (2) Bilateral hip involvement which is an indication for arthroplasty, prosthesis, or mold, because of the possible eventual necessity of surgery on the opposite hip. (3) Sedentary occupations because patients value motion more than stability. (4) Coxa-vara. This anatomical direction of the neck and head is most ideal for a prosthesis since the possibility of dislocation is slight and motion can be instituted early. Also, weight bearing on the prosthetic device is distributed over a greater surface area than when the prosthesis is in a valgus position. (5) Avascular necrosis of the femoral head in which prosthetic replacement is preferable to a mold since the

Fig. 11.

Fig. 12.

Fig. 11. A pre-Judet arthroplasty of a patient who had a previous osteotomy for a malunion fracture of the neck of the femur.

Fig. 12. Poor end result, the amelioration rate being only 4. This case was unsuitable for any type of arthroplasty.

mold often migrates due to absorption of the femoral neck. (6) Normal acetabulum because when the cartilaginous surface of the acetabulum is relatively intact and no reconstructive surgery is necessary, the convalescence is surprisingly rapid. (7) A long femoral neck which is essential in the Judet type of prosthesis in order to insert the prosthesis properly and obtain adequate purchase. It provides sufficient distance between the greater trochanter and the acetabulum, thus permitting adequate abduction motion. Where there is no femoral neck a type of prosthesis, having a preformed neck, may be used. Figure 8 shows one of these prostheses (Austin Moore) which was inserted because of osteoarthritis of the hip.

Absence of the femoral head requires replacement of a weight bearing surface, most efficiently obtained by a replacement prosthesis. A Smith-Petersen mold placed on top of the greater trochanter may be used but the results have not been entirely satisfactory.

Figure 9 is the preoperative film of a patient on whom an arthroplasty of the Judet type was performed. Figure 10 is the follow-up film at the end of 1 year, at which time the amelioration rate was 10.

Contraindications. The replacement prosthesis is contraindicated in: (1) The young age group. Because the follow-up period is so short and the long term results are not known it seems highly questionable whether a young patient should be subjected to this procedure, until a 10 or 15 year follow-up is available. When arthroplasty is indicated in a young patient it would seem best to depend upon a long term, proved method, such as mold arthroplasty. (2) The manual laborer. It would seem that arthrodesis is the best procedure for one engaged in work requiring prolonged standing or walking. (3) Osteoporosis of the femoral neck which affords poor fixation for the stem of the prosthesis. One is, therefore, hesitant in using the type of replacement which depends upon cortical femoral neck fixation for its stability. Loosening of the prosthetic device on the femoral neck several years after insertion has been reported. Associated aseptic necrosis may be primary or secondary in these cases. This complication was not encountered in the present study. Long term follow-up results will undoubtedly indicate the frequency of this complication. (4) Coxa valga. When a prosthesis is inserted in this type of hip the propensity for dislocation is greater than with a Smith-Petersen mold where motion occurs between the mold and the head and between the head and the acetabulum. Also, in a coxa valga type hip there is greater focal pressure between the prosthesis and the acetabulum and this will produce pain. (5) A shallow acetabulum. This requires considerable reconstruction and the mechanical adaption of the two gliding surfaces is better established by an interposed gliding substance, such as vitallium mold. (6) Unusual complications, such as paralysis, poliomyelitis, muscular dystrophies, and myositis ossificans, and previous sepsis all of which militate against any type of arthroplasty.

Figure 11 shows a preoperative film of a patient on whom a Judet arthroplasty was performed. The patient refused a recommended arthrodesis because of 2 previous unsuccessful operations. Figure 12 shows the end result which was only fair—the amelioration rate was 7.

CONCLUSION

In conclusion it must be realized that the indications and contraindications which are tabulated in this article are impossible to evaluate to the letter. As is always true, sound clinical judgment and experience are of utmost importance in determining the correct procedure for the individual patient.

THE PRESERVATION OF LIVING BONE IN PLASMA

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WITHIN the past decade several methods of preserving human bone for grafting have been devised. These methods have taken a very definite place in orthopedic surgery and are serving many useful purposes. It is the purpose of this paper to show that living bone may be preserved for grafting for long periods of time in plasma; and that this bone will not only keep its cellular elements intact but will also show histologic evidence of viability.

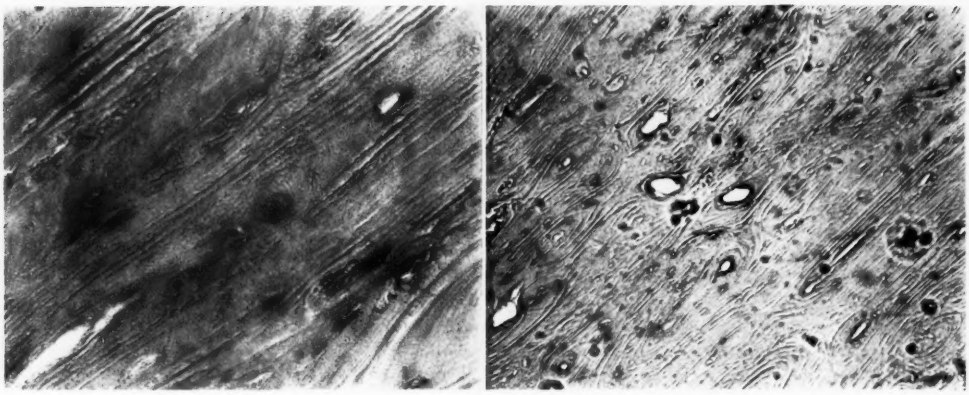
"Latent life" as a term was used by Leeuwenhoek soon after he devised the microscope, when he observed that some microscopic forms of animal life could be arrested by drying and then restored to normalcy by the addition of proper amount of moisture and warmth. Paul Bert successfully transplanted portions of the rat which had been preserved for several days in a controlled temperature of 12 degrees C. (54 degrees F.). In 1912, Alexis Carrel demonstrated the use of frozen bone in grafting and, in 1942, Inclan reported a method of preserving bone in citrated blood for 30 days.

Several years ago it was found by the author that bone of a dog could be kept in the serum of the host at a mean temperature of 5 degrees C. for as long as 18 months and transplanted into other dogs with success. Figure 1 shows a graft of a dog 3 months postoperatively; this graft had been preserved in dog serum for 18 months.

Here it can be seen that the graft has united and has practically the same appearance on the x-ray film as the normal bone. It was also observed grossly that the periosteum of this bone became greatly thickened, and on microscopic sections the osteocytes were found to be present in the lacunae. During the course of this animal experimentation, human plasma was substituted for the dog serum because of the greater availability of the former. However, it was noted that there was no change grossly in the dog bone, the osteocytes soon disappeared from the lacunae, when the animal bone was preserved in human plasma. Figure 2a is a high power photomicrograph of dog bone after being in dog plasma for 18 months; here it is noted that the osteocytes are present in the lacunae. Figure 2b is a low power photomicrograph of dog bone preserved in human plasma for 6 months; here it is noted that very few osteocytes are present.

The method of preserving homologous animal grafts in homologous serum having been successful, similar methods were used for human bone and human plasma. The bone was obtained from fresh cadavers not longer than 6 hours post mortem. These bodies were known to be free from any apparent infection or malignant disease. The blood Wassermann, group, and Rh factor were determined in each case. The entire diaphysis of the tibia was removed with sterile operating room technique and placed in a sterile container. The container was then filled with normal human plasma, and 3 grams of sodium sulfathiazole and 1,000,000 units of soluble

Fig. 1. X-ray photograph of an onlay graft over a fracture of the tibia in a dog. This graft had been preserved in dog plasma for 18 months at 5 degrees C. Note the union of the graft at the end of 3 months.



a b

Fig. 2.

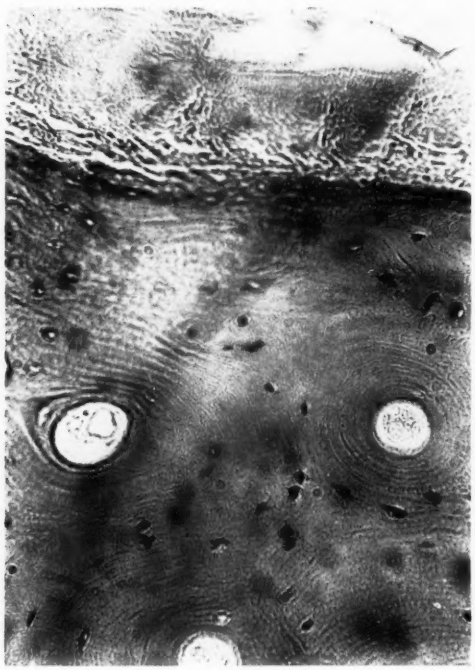


Fig. 3.

Fig. 4.

Fig. 2. a, Photomicrograph (×190) of a dog bone that had been preserved in plasma of the dog for 18 months. This shows the presence of osteocytes in the lacunae. b, Photomicrograph (×90) of bone from the same animal that had been preserved in human plasma for 6 months under the same conditions. This demonstrates the absence of osteocytes from their lacunae.

Fig. 3. Photomicrograph (×125) of human bone, Jenner's and Giemsa's stain. This bone had been preserved in human plasma for 28 months at 5 degrees C. Note the osteocytes present in the lacunae after this length of time.

Fig. 4. Fixed microscopic section (×250), Giemsa's stain, of human bone after 7 days in frozen bone bank. Note the diminished number of osteocytes in the lacunae.

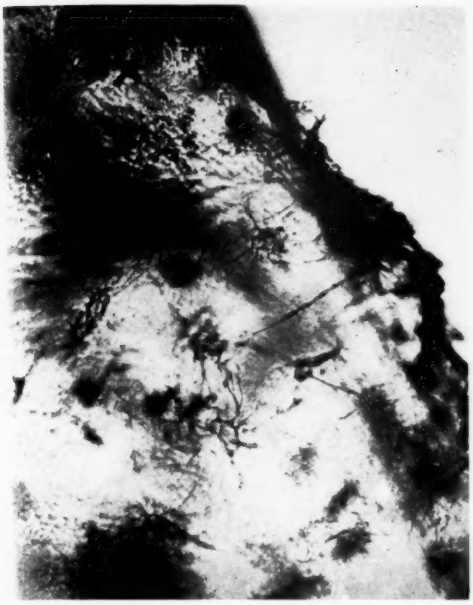


Fig. 5. Photomicrograph (×150) of human bone, supravital stain of neutral red. This bone had been preserved in human plasma for 28 months at 5 degrees C. Note that the dye was not absorbed by the osteocytes, showing the inability of the cells to differentiate this dye.

Fig. 6. Photomicrograph (×150) of human bone, supravital stain of neutral red. This is the same bone as sections shown in Figures 4 and 5 after this bone had been devitalized by dehydration, showing the granules and the cytoplasm of the osteocytes.

penicillin were added to each 1,000 cubic centimeters of plasma for bacteriostasis. The containers were kept at a mean temperature of 5 degrees C. (40 degrees F.). The plasma was cultured initially 1 week after storage and thereafter every 2 weeks for sterility. By this technique no infection was encountered with the exception of 1 specimen which was found to be contaminated by a fungus after 14 months of storage; 2 segments had been taken from this bone previously and used as onlay grafts without any postoperative complication.

MICROSCOPIC STUDIES

Routine laboratory technique for bone sections, such as decalcification with nitric acid and staining with hematoxylin and eosin, was found to be inadequate for this study. The sections used for these specimens, after fixation for 48 hours in 10 per cent formalin, were decalcified with formic citrate solution and stained with Jenner's and Giemsa's stain differentiated in 95 per cent ethyl alcohol, or a modification of this stain suggested by Evans and Krajian. Fixed sections of human bone which had been in human plasma for 28 months showed the structure of the bone to be intact and the osteocytes present in the lacunae in large numbers, with good bone structure comparable with fresh bone (Fig. 3). Bone stored by freezing for a period of only 1 week showed very few osteocytes with very poor bone structure. We realize, however, that despite the large percentage of osteocytes present in bone stored in plasma, this in itself was not sufficient evidence of viability. Supravital staining was used for this purpose instead of the biochemical methods such as the Warburg apparatus, the latter being considered impractical because of the large quantity of finely divided human bone being required for this purpose and the damage inflicted on the osteocytes in the preparation of the specimen

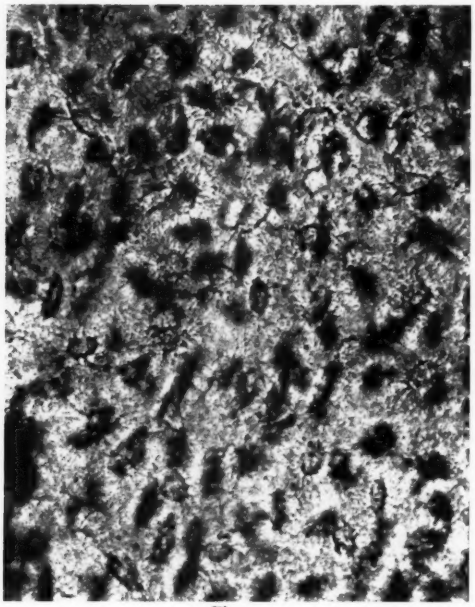


Fig. 7.

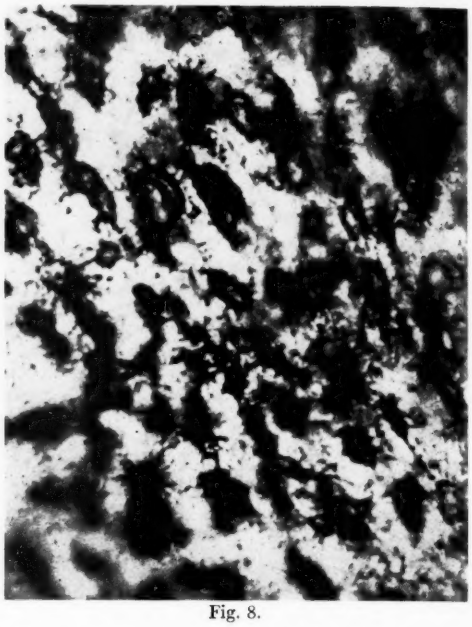


Fig. 8.

Fig. 9.

Fig. 7. Photomicrograph (×150) of a skull plate of a living mouse, supravital stain of neutral red, showing the ability of these living osteocytes to differentiate the dye.

Fig. 8. Photomicrograph (×150) of the same bone shown in Figure 7 after the cell had been devitalized by dehydration, showing the staining of the granules and the cytoplasm of the osteocytes.

Fig. 9. Photomicrograph of tissue culture (×295) of human bone that had been stored in human plasma for 28 months at 5 degrees C., demonstrating structures resembling osteocytes found outside of the bone.

for these determinations. As described by Cappell, in the case of healthy living cells the nucleus and the cytoplasm do not become stained when exposed to supravital dyes, the cells possessing sufficient viability to differentiate the dye. However, in dead or severly injured cells the granules and the nuclei must become stained, the cells having lost their power of differentiation, thus showing the difference between healthy and injured or killed cells. To demonstrate this staining effect upon the stored bone, small slices of human bone that had been kept in human plasma for 28 months were stained with supravital (neutral red). It was found that the osteocytes in this bone did not stain, or possessed sufficient viability to differentiate the

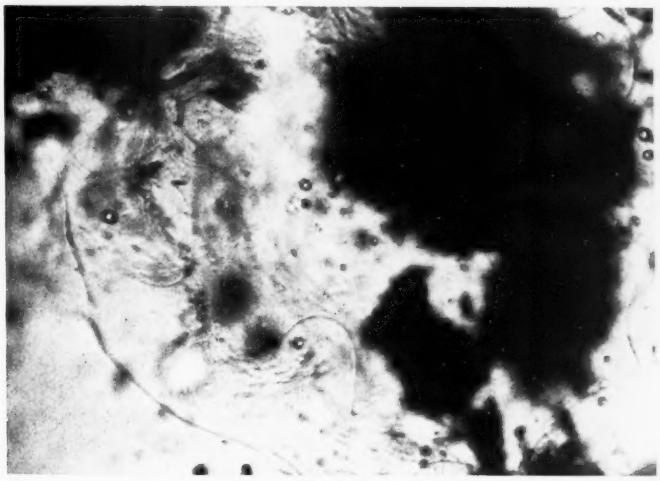


Fig. 10.

Fig. 11.

Fig. 10. Photomicrograph (×295) of tissue culture of human bone that had been preserved in human plasma for 28 months at 5 degrees C., demonstrating coiled elastic and collagenous fibers extending out from the bone.

Fig. 11. Photomicrograph (×295) of tissue culture of human bone that had been preserved in human plasma for 28 months at 5 degrees C., demonstrating coiled elastic and collagenous fibers in the formation of a meshwork outside of the bone.

dye (Fig. 5). The osteocytes were then injured by immersing the same slices of bone in heated glycerine. The dehydration thus produced so injured the cells that they were very definitely stained (Fig. 6). The staining reaction of these cells was then compared to known living osteocytes of a young mouse. Similar results were obtained with these cells as with the osteocytes of the stored bone (Figs. 7 and 8). Wherein the healthy cells did

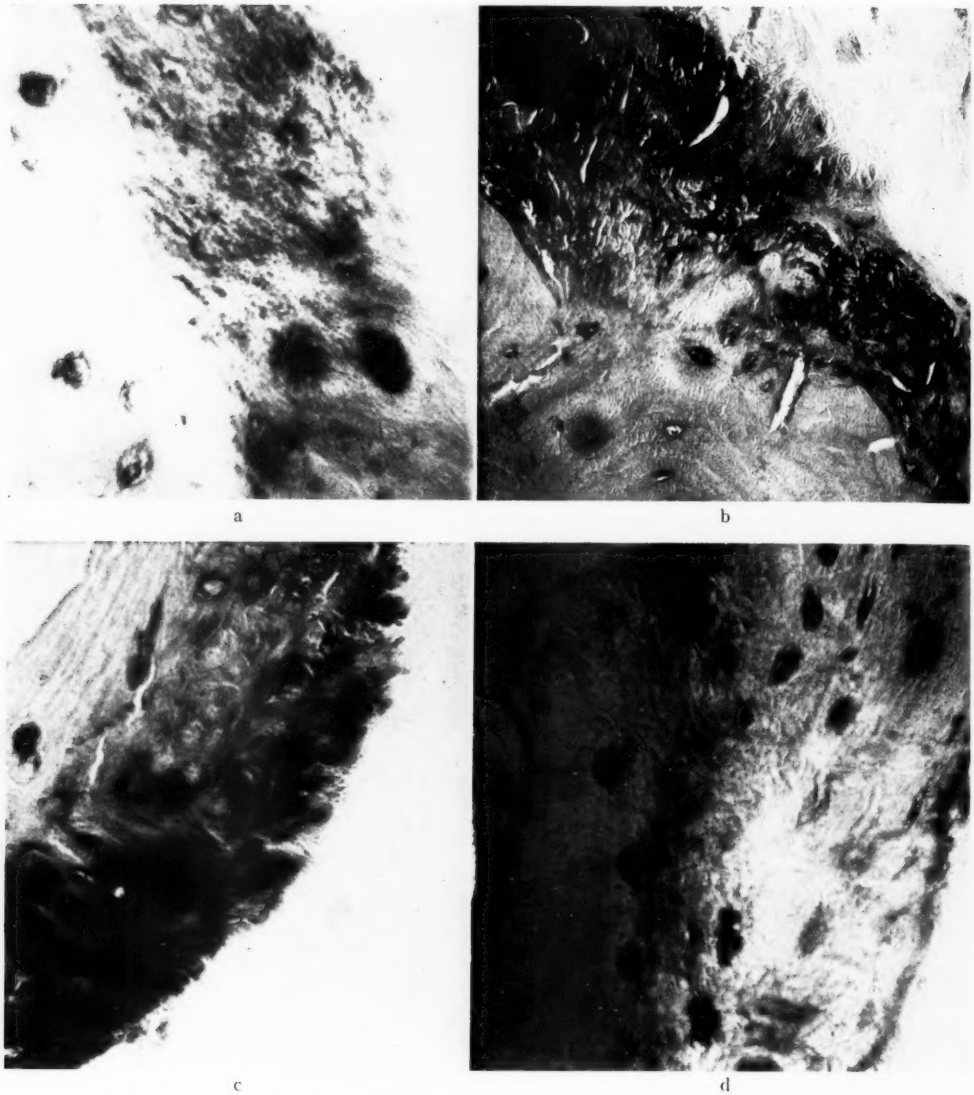
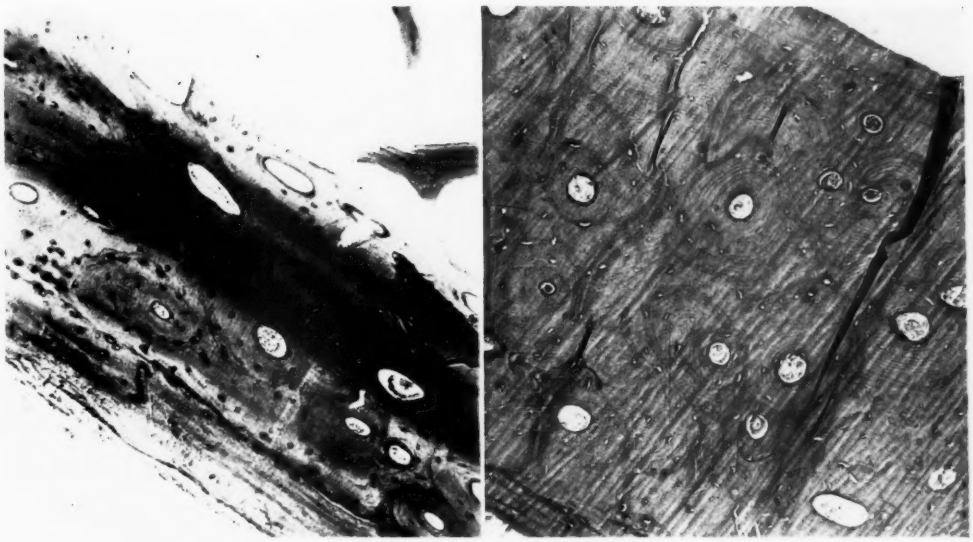


Fig. 12. a, Photomicrograph (×335) of human bone that had been preserved in human plasma for 30 days at 5 degrees C., then incubated at 37.5 degrees C. for 1 month, showing the formation of a fibrillar network with the deposition of mineral granules. b, c, and d, Photomicrographs of the same bone after incubation at 37.5 degrees C. in plasma for 2, 3, and 4 months, showing an increased growth similar to that seen in early bone proliferation.

not stain, however, after injury to these cells by dehydration the granular cytoplasm and the nuclei, in addition, became definitely stained.

TISSUE CULTURE

Inasmuch as the stored bone had shown this evidence of viability by the use of supravital dyes, tissue cultures were then used to



a b

Fig. 13.

Fig. 14.

Fig. 15.

Fig. 13. a, Photomicrograph (×375) of human bone that had been stored in human plasma for 1 month at 5 degrees C., then incubated in fresh plasma at 37.5 degrees C. for 3 months, demonstrating the large percentage of osteocytes present after this length of time at the elevated temperature. b, Photomicrograph (×375) of the same bone after 5 months' incubation in human plasma at 37.5 degrees C., showing marked decrease in percentage of osteocytes.

Fig. 14. Three and one-half month postoperative x-ray film of an onlay graft of a tibia. This graft had been stored in human plasma at 5 degrees C. for 4 months. Note the similarity in density of this graft and the normal bone.

Fig. 15. Three and one-half month postoperative x-ray film of an onlay graft of the humerus. This is an autogenous graft showing a similarity in density to normal bone 3½ months after grafting.

Fig. 16. Six months postoperative x-ray of an onlay graft of the tibia. This graft had been preserved in human plama for 2½ months at 5 degrees C.

Fig. 17. Roentgenogram of the same case as illustrated in Figure 16, taken approximately 2 years subsequently.

observe the behavior of this bone further. Small pieces of the human bone that had been stored in plasma were made into tissue cultures by using a mixture of chicken embryo extract and human placental tissue. These were incubated at 37 degrees C. and examined for a period of 2 weeks. At no time was an osteocyte seen to migrate out from the bone as was to be expected, for they could not come out of the bone lacunae. However, structures similar to osteocytes (Fig. 9) were found outside of the bone; these were probably released from their lacunae after cutting the bone. Many of the cultures showed that both collagenous and elastic fibers had not degenerated, and the coiled elastic fibers indicated that the elastic fibers had not lost their elasticity. This is demonstrated in Figures 10 and 11, where this growth can be seen along the margin of the bone forming bundles and an osteoid growth.

TABLE I.—CHEMICAL CHANGES OF PLASMA COINCIDENT WITH INCUBATION

Incubation period,* month	Calcium mgm. per cent	Phosphorus mgm. per cent	Alkaline phosphatase Bodansky units
0	10.8	3.1	12.9
1	11.2	3.4	9.2
2	18	9.2	2.8
3	13.2	6.3	6.4
4	12.4	4.5	6.5
5	11	5.	2.2
6	10.7	3.4	8.4

*Bone stored in plasma 1 month at 5 degrees C., then placed in fresh plasma each month and incubated at 37.5 degrees C.

To observe the osteogenic properties of bone in vitro which had been stored in plasma, a section of human rib that had been removed subperiosteally at operation was placed in normal human plasma. This was stored by the previously described method at a mean

Fig. 18. Photomicrograph (×100) of the same case as shown in Figures 16 and 17. This was taken from the graft approximately 2½ years postoperatively and shows replacement of the graft with normal bone.

Fig. 19. Roentgenogram of an onlay graft of the tibia taken 6 months after the operation. This graft had been preserved in human plasma at 50 degrees C. for a period of 11 months.

temperature of 5 degrees C. for a period of 1 month. After 1 month in storage this bone was then removed, placed in fresh human plasma, and incubated at 37.5 degrees C. Portions of this bone were taken at monthly intervals for microscopic sections and the stored bone was then replaced in fresh human plasma. Controlled chemical determinations were simultaneously made on the plasma in which the bone was being incubated. The microscopic sections of this bone, which had first been stored for 1 month in plasma and then incubated at body temperature in fresh plasma, show a histologic picture of the changes that are very similar to those changes that occur in normal bone proliferation. In the early stages the bone cells appear to be larger, markedly basophilic with a decided hypertrophy of the Golgi apparatus. As is demonstrated in Figure 12a, these cells are enmeshed in their fibrillar deposition in which mineral granules are being formed. At the end of the second, third, and fourth months (Fig. 12b, c, and d) the fibrils became more dense, the cells are arranged in surface rows with an increase in density of the formation.

CHEMICAL FINDINGS

When bone was stored in plasma in the proportion of 1 part bone to 4 of plasma by volume for a period of 1 year, at a mean temperature of 5 degrees C., the following chemical changes were noted in the plasma: the calcium increased from 10.7 to 17.1 milligrams per cent, phosphorous increased from 3.6 to 10.2 milligrams per cent, and the alkaline phosphatase decreased from 2.63 to 0.7 Bodansky units. The hydrogen ion concentration increased from a *p*H of 7.4 to a *p*H of 8.2 which was not considered significant because of the alkaline reaction of the antibiotic agents added to the plasma.

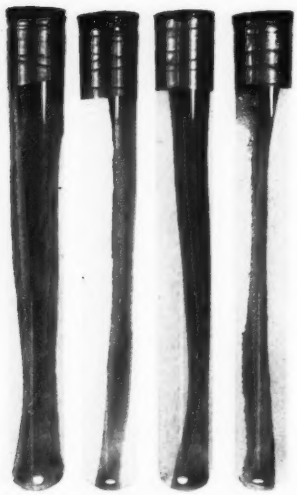


Fig. 20. Four sections of human tibia stored in plasma, demonstrating the described type of containers.

The chemical changes of the plasma coincident with the incubation of the aforementioned bone are shown in Table I. As previously stated, this bone was stored in plasma for 1 month at 5 degrees C. and then placed in fresh plasma each month and incubated at 37.5 degrees C.

It is noted that after the fifth month of incubation there was very little chemical change in the plasma; in correlation with this, it was also observed that the percentage of osteocytes had markedly decreased after the fifth month. Figures 13a and 13b are photomicrographs of this bone taken after 4 and 6 months respectively; the sections made at 4 months show as many osteocytes present as in normal bone and the sections at the end of 6 months are practically devoid of osteocytes.

CLINICAL USE

The use of this type of bone for grafting has thus far proved successful, with results comparable to autogenous bone. This type of preserved bone has been used in 40 cases. In no instance was there a postoperative infection nor a nonunion of the graft. The longest time that a human graft was stored by this method was 11 months. Figures 14 and 15 are postoperative roentgenograms of two types of grafts. Figure 14 is the 3½ month postoperative x-ray film of an onlay graft that has been stored in plasma for 4 months. Figure 15 is the 3½ month postoperative x-ray film of an autogenous graft. It can be noted that both of these grafts have about the same x-ray density as the normal bone.

It is not known definitely when this type of graft becomes a part of the host, however. 1 patient was operated on 6 weeks after grafting and the graft firmly united to the bone that it had been affixed to. Roentgenologically these grafts are well united at 6 months. Figure 16 is a roentgenogram taken 6½ months after grafting, the graft having been preserved in plasma for 2½ months. Figure 17 is a postoperative roentgenogram of this same case approximately 2 years later. This shows good x-ray evidence of bony union. However, these roentgenograms were not considered sufficient evidence of bony replacement. Biopsy of this graft at this time showed complete replacement by normal bone as seen in the photomicrograph in Figure 18. Figure 19 is a postoperative x-ray film taken 6 months after grafting, the graft having been preserved in plasma for 11 months. Both of these show evidence of union of the graft to the host.

PRESENT METHOD OF PRESERVING HOMOLOGOUS GRAFTS IN PLASMA

The bodies from which this bone is removed (whether post mortem or amputated extremities) must be carefully selected especially with regard to infections and malignant disease. Blood for Wassermann, blood type, and Rh factor should be taken. The bone selected is usually the diaphysis of one of the larger long bones, often the tibia because of its accessibility. This is removed under strict operating room technique and the bone is severed from its metaphysis, usually by means of a Gigli saw. After the bone has been removed it should be divided longitudinally in such a manner as to have a maximum amount of bone surface exposed to the plasma.

A sharp, sturdy hand bone saw should be used in dividing this bone, for a motor driven saw of either type generates sufficient heat to

destroy the cellular elements of bone for 4 to 6 millimeters on either side of the blade. It is preferable to wash the marrow from the bone segments before storage with normal saline. The divided bone is then placed in separate tubes and the tubes filled with plasma, the proportion of bone to plasma should be roughly 1 of bone to 4 parts of plasma by volume. Three grams of sodium sulfathiozole and 1,000,000 units of penicillin are added to 1,000 cubic centimeters of plasma. The tubes are closed with a rubber stopper covered with plastic, and sealed with a plastic cap (Fig. 20). The tubes are then stored at a mean temperature of 5 degrees C. (40 degrees F.). The plastic cap is removed when desired and plasma withdrawn through the rubber cap with a needle and syringe, with usual sterile precautions, for culturing. Cultures are usually run 7 days after storage and whenever necessary to check the sterility of the bank.

SUMMARY

Human bone has been preserved in plasma for long periods of time and its cellular elements have remained intact.

The osteocytes of this bone show histologic evidence of viability for as long a period as 28 months.

Chemical changes take place when bone is stored in homologous plasma that do not occur when bone is preserved in heterogenous plasma.

Bone preserved in plasma for a period of 11 months has been used clinically with results which are comparable to those of autogenous bone.

Bone stored in plasma is readily cultured for sterility with maximum assurance against the presence of infective organisms in the bone graft.

Large quantities of viable bone which possesses osteogenic properties can be preserved by this method.

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SURGERY AND PHYSICAL CHEMISTRY

THE thoughtful surgeon is more impressed with the larger bulk of unknowns in his field than he is with the knowledge which has been accumulated. He is also impatiently desirous that all research be culled for items which will add to his usefulness. Eagerness to bring the latest scientific information to practical application at the operating table or bedside has resulted in misdirected steps in occasional instances. Sometimes retreat from the misdirection is possible because there are readily recognizable evidences of error. Unfortunately when in some other instances the false step is not recognizable as such, the difficulties may be compounded, and we find ourselves in the position of treating the therapeutic effort or, as has been said, "in the realm of pathology of therapy." The surgeon is most apt to be trapped into false moves when he is dependent exclusively on reports of complicated laboratory tests for decisions on management.

The field of the biochemistry of water and electrolytes is full of pitfalls. In the first place, we have been made aware of the importance to life of the cell of a very precise water content, water in which are distributed particles with electrochemical activity also of a very precise nature. Furthermore, the area surrounding the cell must be a watery solution of electrochemically active particles of a slightly different nature than those inside the cell. We are told that there is a constant process of interchange and exchange across the membrane which encloses the cell, such interchange being of a highly selective nature. We are now deeply into the physical chemistry of life. To understand what is going on and to converse about it we must use another scientific language, familiar in some degree to the younger amongst us, but rapidly expanding beyond their ken. To our own terms, suture and excision, ligature and clamp we must add millimol, partial pressures, diffusion and dialysis, semipermeable membranes, the laws of mass action. This situation is a good example of the unity of science and the lack of boundaries therein when applied to man's welfare. The explanation of the phenomena with which the surgeon must deal and research into mechanisms is the province of the chemist. The chemist-surgeon or the surgeon-chemist is a rare individual, although it is certainly more compelling for the surgeon to be delving into chemistry than for the chemist into surgery.

For those surgeons who would examine beyond the acceptance of a name or a label as an established fact, *Topics in Physical Chemistry* by W. Mansfield Clark is recommended.

To use new information regarding the biology of water and electrolytes the surgeon

wants the principles stated in such a way that he can formulate rules or laws which he can apply. As Clark writes, a law in physical science is "expressable by a statement that a particular phenomenon always occurs if certain conditions are present. It is not easy always to keep in mind the 'certain conditions'." These conditions, so changing, so indiscernible, so complex, in the human being are "the usual source of error and misunderstanding." In his attempt to present physical chemistry in an elementary form Clark's first sentences are a warning to "those who use a well established law beyond the limits of its applicability." The laws are "limiting laws."

Consider the phenomenon of osmosis—the process of migration of a solvent through a membrane. Osmotic pressure, a derived term to describe another phenomenon, not necessarily related to osmosis, is a measure of the escaping tendencies of the solvent on the two sides of a semipermeable membrane. We are inclined to grasp for a law which we can apply interpreting this process as the mechanism of transport across a capillary, a cell membrane, or an absorbing surface—something we wish to know a great deal more about.

Judge how far the physical chemist is from an explanation of transfer of a solvent across a membrane, even though he may arrange the "certain conditions" under which a limiting law can be written, from this direct quotation from Clark: "It might be a gas phase through which vapor passes; the intervening phase might function by dissolving the solvent molecules from one side and giving them up on the other side; it might absorb the solvent molecules in a reversible chemical reaction running in one direction at one face and in another direction at the other face; it might contain holes, 'pores' of a size that can be penetrated by solvent molecules and not by solute molecules."

Add to the "certain conditions" some of the factors which we know play a part in the body mechanism: gastrointestinal hormones, energy-producing cells lining the membrane, adrenal cortical activity, the complexity of solute and solvent in body fluids, and probably most powerful, but least understood, the demands of a living cell. A law based on the mechanism is pretty remote. An estimate of the situation from any practical laboratory procedure is also far off.

Many methods of measuring so-called extracellular fluid are being explored. These are exacting procedures which measure some body fluid in which dilution of a specific substance takes place and the extent of which is measured at the moment when the sample is drawn. The dynamics of redistribution of such fluid is so rapid that within minutes the volume may be greatly changed. Also, many of the methods fail in the grossly disturbed fluid states in which we are interested. The use of such information as a basis for treatment may lead the overzealous scientific surgeon into greater difficulties.

All this should in no way deter us from setting up guiding principles for the management of water and electrolyte shifts or losses which accompany surgical diseases or are created by surgical operations. The rules must be based upon well grounded empirical facts however, for rules derived from a knowledge of the basic mechanisms are for the future, or in the minds of physical chemists.

There are time-honored, simply obtained facts regarding water and electrolytes which are useful to us. The flame photometer (which some one has described as "a very easy and rapid method of obtaining the wrong answer") is not an indispensable part of the equipment. Neither are we wholly dependent on a laboratory technician performing very complicated analyses for these facts.

Experienced and thoughtful surgeons have used simple measures for obtaining factual information which is invaluable. For instance, Wangensteen considers the body weight of a postoperative patient, when measured on a 100 gram accuracy scale, to be more trustworthy than laboratory methods in controlling ever hazardous overhydration; he estimated blood loss at operation by increase in the weight of the sponges used. Some little thought added to the knowledge of small changes in body weight, measurements of abnormal body fluid losses, fluid intake, urinary output, and specific gravity of the urine can result in a fairly sound idea of the state of hydration. Moyer has written a manual of fluid balance in which the clinical manifestations of types of fluid and electrolyte derangements are stressed because "laboratory data cannot adequately serve as the sole basis for fluid and electrolyte therapy."

It might appear that it would be helpful if we could conduct ourselves on the basis of an objectively derived set of laboratory determinations. This appearance is false, however, because it actually would be corrupting. Surgery is still a pursuit of inquiry. We cannot avoid the exertion of thinking in any experiment we conduct, and all our operations are experiments in treatment. It is unfortunate that the adjective scientific when applied to a surgeon suggests the application of a special branch of science, such as chemistry or physics, by this surgeon. There is also a fund of knowledge which is not expressed in millimols but which is nonetheless surgical science. An experienced surgeon can be speaking the truth, and science is truth, when he says "this patient needs water." His conclusion may be reached by consideration of such impious data as a complaint of thirst, sunken eyeballs, changes in body weight and urine output rather than measurement of total body water and extracellular fluid. He is even so a scientist. JOHN H. MULHOLLAND.

THE RESPONSIBILITY OF THOSE WHO TEACH

THE past 25 years have witnessed an amazing development in American facilities for graduate training in surgery. With over twice as many approved facilities for advanced surgical training in hospitals, there has been a striking increase in the number of surgeons now charged with training those who will be the surgeons of tomorrow.

Basic changes have occurred with these developments. Not only are many more men concerned with the direction of our graduate training but it has become much more widely dispersed since it has broadened beyond the confines of our university hospitals and established clinics to which formerly it was limited. This has had advantages in that the abilities of many competent surgeons throughout the country have been enlisted in the essential teaching program and their cumulative experience is being passed on to the men in training. In return, the caliber of hospital care has improved dramatically with the contribution of these residents in constant hospital attendance.

For those who teach in the daily practice of surgery, it is worth while to consider what should be expected in return for the assistance, patient care, and endless hours of work given each year in our hospitals by those who comprise our intern-resident group in training.

It must be assumed that the salary inducement cannot be considered; nor can the thought that young men have the privilege of seeing how surgical patients are handled be accepted as compensation in full.

The writer believes that the responsibilities of those who direct young men in their training may be considered in three categories: (1) to provide fundamental training in sur-

gical diagnosis and the technical aspects of surgery; (2) to instill an appreciation of the responsibilities and obligations of the surgeon to the patient, his colleagues, and to society; (3) to impart those intangible assets which are acquired with experience from mentor to assistant so that he may have both the background and the courage to meet the problems which beset all in surgical practice.

In the modern hospital with its trained staff and many facilities, an adequate background in surgical diagnosis, preoperative and postoperative care, and surgical technique is being accomplished on a higher plane than ever before. This fundamental responsibility is being discharged in the vast majority of our teaching centers to the credit of the profession and the advantage of the public. It is primarily of the other two cardinal obligations that comment seems in order.

In this highly scientific era we hear less and less discussion of the responsibilities and obligations of the surgeon to the patient and to society. It has long been accepted that in judging the stature of a surgeon paramount importance should be placed upon his capacity to train great disciples. Lord Moynihan had this in mind in the first Murphy oration: "It is the inspiration, the lofty sense of a sacred mission worthy of the best that is in you, the dedication with humblest and fullest devotion to the cause of scientific truth and of loyal service to mankind, that are awakened with a thrill in great men by great teachers."

Is this too high an ideal to ask of the busy surgeon in his daily round of pressure? Consciously perhaps, but by precept and example it is being accomplished in endless centers and with a little thought it may be better served.

The third facet of training concerns those intangible assets that come to those privileged to serve under great teachers. My surgical chief, the late Eldridge L. Eliason, was one who understood this phase of teaching and succeeded in a remarkable way in imparting his wisdom to a generation of students, interns and fellows at the University of Pennsylvania. The aphorisms which were part of our daily life during training days were helpful at the time, but the succeeding years brought them into real focus as fundamental guides in difficult situations. Never a week passed without some time being given to a discussion with his fellows of the art of surgery, for he believed that science alone was insufficient.

Of all the intangible assets, moral courage is probably the greatest one to be openly discussed and fostered by the surgeon in his training contacts with residents. His responsibility here is comparable to that of father with son, and by precept his is a grave obligation. A frank discussion during the training days of the problems and temptations of unethical practice with a clear-cut program for avoiding its pitfalls would do much to dispel and control these issues. This can be done more realistically than formerly since so many who teach are actively engaged in private practice.

Surgeons of above average ability are those who sense promptly a patient situation that is unsatisfactory and immediately avail themselves of any consultation that will assist in clarifying the problem. This concept of the occasional inadequacy of the individual must be clearly demonstrated to our younger associates so that this precept will be followed promptly and without embarrassment.

Finally, the great teacher is he who will admit the existence of real problems in his own experience and through counsel, encouragement, and example help those whom he trains to surpass those who teach. If this be accomplished we will have built a living memorial which will grow with succeeding generations in keeping with the highest traditions of our trust.

CHARLES W. MCLAUGHLIN, JR.

THE SURGEON AT WORK

REMOVABLE FOAM RUBBER OBSTETRIC FORCEPS COVERS

EMANUEL M. GREENBERG, M.D., New York, New York

OBSTETRIC instruments in use even as late as the middle ages were indeed crude and destructive. The obstetrician of old had more instruments at his disposal to extract a dead child than a living one. The chief reasons for this were that obstetric instruments had not yet been refined to the point where they could be used with safety on the living child; besides, the obstetrician was usually called in only after the midwife had exhausted all her patience, when the baby or the mother was dead or dying. With the rise of such men as the Chamberlens, Jean Palfyn, and William Smellie, more emphasis began to be placed on the safe extraction of a living child. Since then obstetric forceps have undergone an evolution from instruments of crude brutality to instruments of safe dependability. Another step toward achieving that ultimate objective will be presented in this paper.

It was realized relatively early in the history of forceps that there was a need for a protective cushioning when the newborn head is the object of a grasping pair of metal prongs. For indeed in Smellie's *Midwifery* of 1763 there are pictures depicting leather covered forceps.

Although Blundell, in his 1834 *Midwifery*, stated: "Cleanliness renders it desirable that the forceps should not be coated with leather," and Ramsbotham, in his 1841 *Midwifery*, stated that obstetric forceps covered with leather "do not pass up so easily" as when they are uncovered, obstetricians were nevertheless thinking along proper lines in the softening of their instruments; but the chemistry of rubber in general, and foam rubber in particular, had not yet arrived. The purpose of this presentation is to introduce a removable, sterilizable, shock-absorbing covering for forceps, which is inserted with ease between vaginal wall and fetal head.

In reviewing a few highlights in the evolution of forceps, it will be recalled that at first the forceps were made into two parts by Chamberlen; then Smellie added the pelvic curve and improved the lock; following this, forceps were covered with leather. In more recent times, the steel has been skillfully rounded off at the edges and the surface highly polished and plated. And then, in this country, the author was the first to suggest rubber-dipped forceps (1). However, the latter did not prove practicable as special chemical priming and other technical procedures, such as the use of fixatives prior to dipping, were involved, and reprocessing was continually necessary after the coating showed signs of wear following re-use and resterilization. Moreover, the dipped forceps do not even approach the softness of foam rubber, and it would be necessary always to have double the number of forceps in the delivery room, in order to have the dipped and the undipped of each type of blade at all times.

Therefore, removable rubber forceps mittens were devised, and foam rubber was utilized for extra softness and compressibility. With the removable foam rubber forceps mittens, the operator uses the mittens or not, according to the dictates of each case. There is no need whatever in increasing the number or the type of forceps in the delivery room. The foam rubber mittens fit all blades. They should be sterilized just as rubber gloves are, and like rubber gloves, the mittens are powdered and placed in separate glove compartments.

DIRECTIONS FOR INSERTING FOAM RUBBER GAUNTLETS ON BLADES

1. Place sterilized foam rubber gauntlets in a basin containing sterile water. (The foam rubber sleeves are easily sterilized in the autoclave at 250 degrees for 15 minutes.)
2. With water still dripping, stretch over each blade, by either inserting the index fingers of both hands or by inserting a ring-clamp (or any suitable instrument handy) to stretch neck of bootee over blade. After stretching neck of bootee over blade, remove instrument. Then complete insertion by pulling down the bootee over the forceps blade manually. (Rubber bands may be placed around the necks of gauntlets to prevent foreign matter from entering.)
3. Press out the excess water after the application.
4. Soap up the rubber coverings on all surfaces and borders.
5. The foam rubber covered blades will now slide in with extreme ease in the usual manner.

From the Department of Obstetrics and Gynecology, Mt. Sinai Hospital, New York, N. Y.

6. During extraction, the gauntlets do not slide off; they remain firmly in place.

The foam rubber forceps mitten converts the proverbial iron hands to the "iron hands beneath the velvet gloves."

They can be used on both solid and fenestrated blades. When used on the latter, they distribute the pressure and homogenize the grasping forceps, blending the steel borders together as it bridges the fenestration while yet retaining the qualities of the fenestration for which the latter was originally designed.

When used on fenestrated forceps, it does away with the potentially dangerous hook effect of the blade, whereby ears have been known to be cut and pulled off.

Following is a classification of forceps injuries which presents in an organized way the injuries to which the instrumentalized newborn has been known to be susceptible.

CLASSIFICATION OF FORCEPS INJURIES (2)

Grade

1 Superficial bruises limited to epidermis.
2 Abrasions extending to subcutaneous tissues; injuries to fascia, muscles, or periosteum; burns from hot, freshly sterilized forceps.
3 Hematomas: cephalohematomas (subperiosteal or supraperiosteal), hematoma of cheeks and neck, orbital hematoma.
4 Nerve injuries: facial nerve, brachial plexus, oculomotor, optic, auditory.
5 Organ injuries: evulsion of an ear, eyelid; eye injury (enucleation of eyeball, traumatic cataract, corneal opacity, abruption of choroid, retinal hemorrhage). Injury to salivary gland or its duct, with possible fistula formation.
6 Cranial bone fractures.
7 Brain and spinal tissue injuries, concussion, and hemorrhages: subdural hematoma, peribulbar hematoma, tentorial tears.
8 Compression or cutting of umbilical cord with asphyxia.

From perusing this classification, it will be seen that foam rubber forceps protectors can be of real help in avoiding many of these injuries. Thus it is hoped that the use of the foam rubber forceps mittens will help reduce the number of forceps injuries and will prove particularly valuable in the delicate process of the training of students, interns, and residents in the use of obstetric forceps.

The foam rubber mittens have been used in over 100 cases with no cuts, marks, abrasions, eye, ear, or any kind of surface injury, thus far. These cases are both low and mid forceps of the Simpson-Elliot type.

We must not permit ourselves to become too proud of our high percentage of unmarked forceps babies, any more than we can become too proud of our maternal mortality record. In the statistics of maternal mortality, the difference of one in a thousand makes the difference between a good and a bad record. Should not the same attitude obtain in approaching the problem of fetal forceps injury?

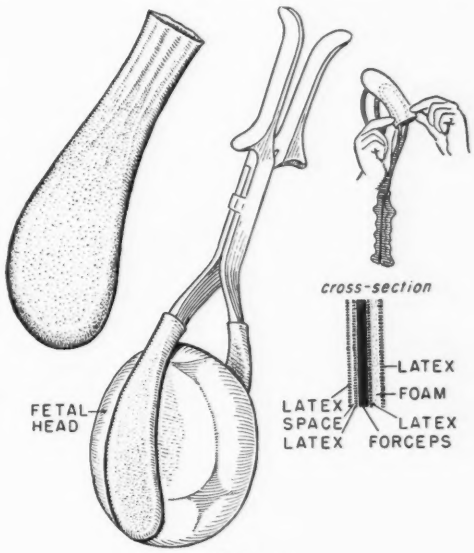

Fig. 1.

Most of us can recall a relative or acquaintance who has had a forceps injury in birth. It is true that better obstetrics is being practiced today than a century or even a decade ago, but even today one need not look too far nor too long to recall a severe forceps injury. In western New York State, about 2 years ago, an infant's eyelid was completely evulsed by a small spur on an imperfectly polished pair of forceps. Had foam rubber mittens been used in that case, that injury would have been prevented.

In addition, foam rubber forceps mittens prevent slipping of the blades which is so dangerous to the baby. The mittens are also very useful in delivering the small premature head. In the low flap cesarean section, through a transverse or semilunar incision of the lower uterine segment, it is often advisable to use but one blade of the obstetrical forceps in order to dislodge a semi-engaged head and thus facilitate delivery. Ricci advocates that the blade so used be covered with a foam rubber mitten, in view of the potentially traumatic vectis or crowbar mechanism involved.

SUMMARY

The application of bare steel to the head of a newborn baby has produced a high traumatic toll ever since the introduction of obstetric forceps. Removable foam rubber protectors for obstetric forceps are presented in the belief that any suggestion is indicated which is calculated to increase the safety factor of our instruments. It is hoped that this new device will relegate obstetric forceps to the role of the "iron hands beneath the velvet gloves" and render them less traumatic to both mother and baby.

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3. RICCI, JAMES V. Personal communication.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE latest edition of an established, well known work *Nutrition and Diet in Health and Disease*[1] retains its original organizational plan, with approximately one-half of its pages devoted to normal nutritional requirements in health and growth, and the remainder of the volume to a presentation of diet requirements in altered metabolic states and disease. A brief, yet adequately comprehensive discussion of pathologic conditions in this field, classified according to systems—metabolic disorders, deficiency and febrile diseases, and nutritional problems in surgery and industry—is included, with the interrelationship of disturbed body chemistry stressed. Thus a rational approach to therapy is presented. It contains numerous charts, tables, and menus, carefully compiled, detailed, and clearly stated, so that practical, economical diet management may be followed. A complete bibliography, which includes recent contributions to the subject as well as classic references, is appended to each chapter. This book may be enthusiastically recommended and should serve as a frequently utilized reference.

EDWARD BIGG.

THE first volume of a two volume work on gynecology, *Gynecology; Diseases and Minor Surgery*,[2] has been compiled and edited by Robert J. Lowrie. The 53 chapters of the present volume have been written by 41 contributors, many of whom are well known gynecologists. The well organized plan followed in presenting each chapter has integrated the material and reduced repetition. In general, the subjects are well covered in brief and concise fashion, the opinions of the essayist and his recommendations reflecting the currently accepted concepts and principles.

The chapters on developmental anatomy and anomalies, endocrine principles, menstrual and cyclic phenomena, disorders of the immature vulva and vagina, and abnormalities of the reproductive and sex functions are deserving of special note. Those on physical therapy, minor surgery, and medications should be particularly helpful because of their practicality. References to the historical and current literature are relatively limited in most of the chapters.

The text is profusely illustrated. Many of the figures, most of which are well reproduced, are original. Those which were not prepared specifically for this text have been carefully selected from pertinent sources.

The arduous task of editing such a work is frequently unrecognized by the reader. Dr. Lowrie has accomplished this admirably, as is evidenced by the uniformity of presentation and by his consolidation of the works of many contributors.

The publisher is to be commended for the excellence of the binding, the paper, and the printing.

JOHN W. HUFFMAN.

IT has been the custom to expect the author of such a specialized work as *Gynecological and Obstetrical Pathology*[3] to be a person who is primarily a gynecologist, an obstetrician, or both. It is therefore a pleasure to read an objective text on this subject written by a general pathologist. This is particularly true when the material is covered as adroitly as it is in the present volume.

An estimated one-third of the gynecologic specimens in the standard hospital tissue laboratory are diagnosed, necessitating a certain amount of competence by the clinical microscopist. It is not always possible to have a joint study by the respective departments of pathology and gynecology as is established in the institutions with which the reviewer is associated. Such a procedure is mutually advantageous. For those who do not have the opportunity, this textbook is even more valuable. It acts as a silent consultant.

Herbut has organized the chapters carefully. He has briefly summarized embryology and physiology. Since he initiated these basic concepts he might have considered a concise review of bacteriology; this has been considered under the separate subjects. His remaining chapters have emphasized the anatomic approach. He adheres closely to a specific pattern of definition, incidence, cause (established or theoretic), gross and microscopic appearance, complications, clinicopathologic correlation, diagnosis, treatment (which in instances may be questioned), and prognosis. By so doing he provides a varied degree of information. As might be surmised, much of the content is devoted to neoplasia. Trauma is included but plays a minor role. The amount of space devoted to inflammation is in keeping with its low incidence of the moment.

[1] NUTRITION AND DIET IN HEALTH AND DISEASE. By James S. McLester, M.D., and William J. Darby, M.D., Ph.D. 6th ed. Philadelphia, London: W. B. Saunders Co., 1952.

[2] GYNECOLOGY; DISEASES AND MINOR SURGERY. Compiled and edited by Robert J. Lowrie, M.A., M.D., F.A.C.S., D-OG. Foreword by Claude E. Heaton, M.D. 1st ed. Springfield, Ill.: Charles C Thomas, 1952.

[3] GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY. By Peter A. Herbut, M.D. Philadelphia: Lea & Febiger, 1953.

His bibliography stresses the literature of this country. It is very much up to date.

The photographs of gross specimens are more comprehensive than photomicrographs. Nearly all are in black and white. Emphasis is on very low magnification, which may arouse criticism from some readers.

There is a chapter on the Rh factor and blood groups. The debatable subject of preinvasive carcinoma of the cervix is discussed in a noncommittal manner. Reference is made to some of the accepted articles. The still current and mistaken concept of a much higher incidence of cervical over corpus carcinoma is again expressed. Some may question the casual discard of Krukenberg's tumor. The high incidence of metastases to ovaries from tumors elsewhere is stressed.

The use of melanoblastoma and lymphoblastoma rather than specific terminology may be open to comment.

However, these are unimportant in determining the quantitative value of the book. Word for word, line for line, and page for page, this text provides an extensive amount of information upon one of the very important phases of disease.

MARK C. WHEELOCK.

THE fact that the *Anatomy of the Nervous System*[1] has now appeared in the ninth edition since its first inception by Dr. Ranson in 1920 attests to the fact that this book continues to be widely accepted as a teaching standard in English speaking countries.

Though Dr. Clark in the last two editions has kept abreast of all the recent developments in neurologic anatomy and its application to function, with the addition of much new material and some rewriting of the old material, nevertheless the original flavor of Dr. Ranson's book has been retained. It was the express purpose of Dr. Ranson's text to make neurologic anatomy a dynamic subject, one to be correlated closely with neurologic function and that in turn with the neurologic problems of the diseases of the nervous system. The book continues to lay stress upon the importance of the details of developmental neurologic anatomy. The minute and beautifully illustrated descriptions of the gross and microscopic anatomy of the brain stem, particularly, continue to be one of the most admirable features of this book. This lucid treatment of the brain stem, and particularly of the contained cranial nerve nuclei, should be a comfort to the student and help him overcome his fear of neurology as a difficult and unattainable subject.

This ninth edition contains many new features in addition to the old effective ones which were Ranson's own. There is a short, concise, well illustrated chapter on the meninges and the blood vessels of the central nervous system. Fresh material has been added on the description of neurones and neuroglia, and the sections on the cerebral cortex summarize in a succinct manner the many recent discoveries in the anatomy and function of that structure since the earliest edition. The section on the application of anatomic levels to clinical syndromes has fortunately been retained and many a former student of this book will remember the interest with which he read these clinical descriptions and first found that his newly gained knowledge of what he thought a hopelessly difficult subject could be applied for practical ends without any insurmountable difficulty. Also the final section containing a laboratory outline of neuroanatomy is still retained, and it has always proved to be an aid to the student in helping him to clarify and correlate the mass of material which the book contains.

Throughout the text there is constant reference to the results of currently developing neurologic research, both in this country and elsewhere, and the bibliography, complete and exhaustive, is well up to date.

Dr. Ranson's preface to the first edition fortunately has again taken its proper place in the present book and as such it is not only a historical marker, but also a tribute to him by Dr. Clark and by all the readers who will cherish this preservation of Dr. Ranson's own words. The book is invaluable to the student and clinician alike.

JOHN MARTIN.

THE book *An Atlas of Skull Roentgenograms*[2] is new, and as such happily fills a long standing need for such an atlas for reference in the daily problems of roentgenologists, neurologists, and neurosurgeons.

Six hundred and three untouched photographs of x-ray pictures drawn from the personal files of the authors, together with a lean, concise text, make this book truly a working atlas. The first chapter is a particularly helpful one, since it illustrates all the normal variations of the human skull in infancy, childhood, and adult life. The section on normal intracranial calcifications should be an aid to the roentgenologist in deciding what type of calcific deposits are pathologic and which are normal variations. Separate sections deal with congenital variations and anomalies, trauma, infections, tumors of both the brain and the skull, and non-neoplastic diseases of the skull.

The illustrations are remarkable for their clarity. Not only is the reproduction of unusual quality, but the original pictures themselves are of such excellence that many a hospital x-ray department could aim at such quality as a goal. Contrast studies, such as pneumograms and arteriograms, are not used. Laminagraphy is apparently a useful and much used technique in the hands of the authors. The photographs are distinctive if for no other reason than for the absence of restraining fingers,

[1]THE ANATOMY OF THE NERVOUS SYSTEM; ITS DEVELOPMENT AND FUNCTION. By Stephen Walter Ranson, M.D., Ph.D. Revised by Sam Lillard Clark, M.D., Ph.D. 9th ed. Philadelphia, London: W. B. Saunders Co., 1953.

[2]AN ATLAS OF SKULL ROENTGENOGRAMS. By Bernard S. Epstein, M.D., and Leo M. Davidoff, M.D. Philadelphia: Lea & Febiger, 1953.

bobby pins, rings, necklaces, safety pins, large serial numbers and hospital tags, adhesive tape, and other commonly included shadows. When one realizes how difficult it often is to search through one's own files for a set of x-ray pictures suitable for publication, the excellence of this atlas can well be appreciated and it is evident that the illustrations must have been drawn from a great mass of fine clinical material.

The inclusiveness of the pathology pictured is too great for detailed mention in a review of the book. One can only say that it is a book to have open on one's desk, not closed and on a shelf.

JOHN MARTIN.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

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A SHORT PRACTICE OF SURGERY. By Hamilton Bailey, F.R.C.S.(Eng.), F.A.C.S., F.I.C.S., F.R.S.E., and R. J. McNeill Love, M.S.(Lond.), F.R.C.S.(Eng.), F.A.C.S., F.I.C.S. 9th ed. 1,254 pages, with 1,234 illustrations. $12.50. Baltimore: The Williams & Wilkins Co., 1953.

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THE SURGERY OF PANCREATIC NEOPLASMS. By Rodney Smith, M.S., F.R.C.S. 157 pages, with 111 illustrations. $7.00. Edinburgh, London: E. & S. Livingstone Ltd.; Baltimore: The Williams & Wilkins Co., 1953.

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DIAGNOSTIC TESTS IN NEUROLOGY; A SELECTION FOR OFFICE USE. By Robert Wartenberg, M.D. Forewords by Sir Gordon Holmes, M.D., F.R.S., and by Stanley Truman, M.D. 228 pages, with 62 illustrations. $4.50. Chicago: The Year Book Publishers, Inc., 1953.

RECURRENT DISLOCATION OF THE SHOULDER. By James A. Dickson, M.D., Alfred W. Humphries, M.D., and Harry W. O'Dell, M.D. 158 pages, with 78 illustrations. $4.50. Baltimore: The Williams & Wilkins Co., 1953.

LE PNEUMOPATIE INFETTIVE DEL FETO E DEL NEONATO. By Giuseppe Valle. 231 pages, with 54 illustrations. Torino: Edizioni Minerva Medica, 1953.

SANDOZ ATLAS OF HAEMATOLOGY. 91 pages, 256 illustrations. Basle: Sandoz Ltd., 1952.

OPERATIVE GYNECOLOGY. By Richard W. Te Linde. 2nd ed. 902 pages, with 409 figures and 7 color plates. $20.00. Philadelphia, London: J. B. Lippincott Co., 1953.

FUNCTIONAL DISORDERS OF THE FOOT; DIAGNOSIS AND TREATMENT. By Frank D. Dickson, M.D., F.A.C.S., and Rex L. Diveley, A.B., M.D., F.A.C.S. 3rd ed. 345 pages, with 205 illustrations. $6.75. Philadelphia, London, Montreal: J. B. Lippincott Co., 1953.

HYPERSPLENISM AND SURGERY OF THE SPLEEN. By William Dameshek, M.D., and C. Stuart Welch, M.D. 84 pages, with 105 illustrations. $10.00. New York: Grune & Stratton, Inc., 1953.

THE CONCEPTION OF DISEASE; ITS HISTORY, ITS VERSIONS AND ITS NATURE. By Walther Riese, M.D. 120 pages. $3.75. New York: Philosophical Library, 1953.

THE FOUNDERS OF NEUROLOGY; ONE HUNDRED AND THIRTY-THREE BIOGRAPHICAL SKETCHES. Prepared for the Fourth International Neurological Congress in Paris by 84 authors. Edited by Webb Haymaker, M.D. With the assistance of Karl A. Baer. 479 pages, illustrated. Springfield, Ill.: Charles C Thomas, 1953.

AN ATLAS OF SURGICAL EXPOSURES OF THE EXTREMITIES. By Sam W. Banks, M.D., and Harold Laufman, M.D., Ph.D. 391 pages, with 552 illustrations on 179 plates. $15.00. Philadelphia, London: W. B. Saunders Co., 1953.

CLINICAL ENDOCRINOLOGY. By Lewis M. Hurxthal, M.D., F.A.C.P., and Natalija Musulin, B.S., M.D. Two volumes. 749 pages, 482 figures, 145 charts, 1 color plate. $24.00. Philadelphia, London, Montreal: J. B. Lippincott Co., 1953.

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CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

HAROLD L. FOSS, Danville, Pennsylvania, *President*
FRED W. RANKIN, Lexington, Kentucky, *President-Elect*

PRELIMINARY PLANS FOR THE 39TH CLINICAL CONGRESS—THE CONRAD HILTON HOTEL, CHICAGO, OCTOBER 5 TO 9, 1953

THE 39th Clinical Congress of the American College of Surgeons will be held in Chicago, October 5 to 9, 1953. This is the 10th Congress in Chicago, recalling the fact that the first Congress was also held in this city: 1,300 surgeons came to the first Clinical Congress of Surgeons of North America on November 7, 1910, in answer to an editorial in the September, 1910, issue of SURGERY, GYNECOLOGY AND OBSTETRICS inviting all interested surgeons to attend a series of operative clinics in Chicago. Chicago was also the setting for the first Convocation of the American College of Surgeons, which met in conjunction with the Clinical Congress of Surgeons of North America until the date of their merger in 1917. Clinical Congresses were held in Chicago in 1913, 1917, 1923, 1929, 1933, 1937, 1940, and 1949.

Registration is expected to approach the 11,526 figure set at the last Congress in New York, for these events, the largest surgical meetings in the world, are synonymous with the highest quality in terms of interest to the profession.

The headquarters hotel, the Conrad Hilton, largest hotel in the world, will house most of the meetings, and all the exhibits. Nearby hotels and auditoriums will also supply needed space. The Clinical Congress makes more demands for meeting rooms than any organization in the country, since we may have as many as 13 to 15 meetings going on simultaneously.

The Conrad Hilton has set aside 1,300 rooms for Fellows which, combined with Chicago's other excellent hotel accommodations, will greatly simplify the housing problem. Because this city is also the transportation center of the nation, representatives from all the travel systems will be on hand to assist with any post-Congress travel plans.

General plans for the Congress, while following those of previous years, have been carefully attuned to current needs of the surgical profession, in keeping with the College policy of making each Congress as useful as possible.

Because of the superiority of the motion picture and TV processes in permitting more surgeons to view operative techniques more satisfactorily, wet clinics have been eliminated this year. Ciné clinics, special three-dimensional films, and new medical motion pictures of current interest will be shown. Two clinicopathology conferences have been scheduled this year, one on Monday afternoon, with Dr. Paul R. Cannon as moderator, and the other on Wednesday afternoon, with Dr. William B. Wartman as moderator.

Since the American Boards of Ophthalmology and Otolaryngology are holding examinations during Congress week, the College's Advisory Councils for Ophthalmology and Otolaryngology have recommended that sessions in these two specialties this year be limited to three evening programs, at which important panel discussions will be heard.

CHICAGO COMMITTEE ON ARRANGEMENTS

The Chicago Committee on Arrangements for the Clinical Congress is composed of the following Fellows:

THOMAS C. DOUGLASS, *Chairman*
STUART ABEL, *Secretary*
J. GARROTT ALLEN, *Publicity Chairman*
LESTER R. DRAGSTEDT, *Television Chairman*
HILGER PERRY JENKINS, *Ciné Clinics Chairman*
CHARLES B. PUESTOW *Hospitality Chairman*

WILLIAM E. ADAMS
PAUL C. BUCY
JOHN M. DORSEY
EGBERT H. FELL
R. KENNEDY GILCHRIST
PAUL W. GREELEY
MYRON M. HIPSKIND
PAUL H. HOLINGER
JOSEPH H. KIEFER
WILLIAM M. LEES
WALTER G. MADDOCK
SAMUEL J. MEYER
JOHN T. REYNOLDS
HERBERT E. SCHMITZ
JAMES K. STACK
JANET E. TOWNE
AUGUSTA WEBSTER
LEO M. ZIMMERMAN

OFFICIAL MEETINGS

Only three general evening sessions will be held this year. At the opening evening meeting of the Clinical Congress, on Monday, Dr. Thomas C. Douglass, Chairman of the Committee on Arrangements, will welcome visitors to the Congress, Dr. Evarts A. Graham, Chairman of the Board of Regents, will introduce guests, and Dr. Harold L. Foss, President of the College will make the Presidential Address. Sir James Paterson Ross, of London, will give the eighth Martin Memorial Lecture, speaking on "Science and Surgery."

On Wednesday evening the scientific session will include the Oration on Trauma, by Dr. William L. Estes, Bethlehem, Pa., and papers on "Cardiac Arrest: Etiology and Management from a Study of Over 1,300 Cases" by Dr. J. William Hinton, New York, and "Metabolic and Electrolyte Abnormalities in Severely Ill Cardiac Patients and Individuals with Advanced Cancer" by Dr. Francis D. Moore, Boston.

The annual meeting of Fellows will be held on Thursday afternoon. The annual Convocation will be held on the final evening, Friday, October 9. Initiates will be presented for Fellowship, honorary Fellowships conferred, and officers inaugurated. Dr. Fred W. Rankin, incoming president of the College, will give the Fellowship Address.

Tuesday and Thursday evenings will be left free for committee meetings, the motion picture symposium, and other special group activities.

PANEL DISCUSSIONS

The general scientific sessions of the Congress will begin this year with a panel discussion on "Management of Gastric Ulcers" at 10:30 a.m. on Monday, October 5. This first session takes the place of the "General Assembly" which opened previous Congresses. Subjects of other general panel discussions follow:

Monday, 3:30–5 p.m.—Carcinoma of the Mouth
Tuesday, 1:30–3 p.m.—Blood Transfusions: Complications and their Management; 3:30–5 p.m.—Polyposis of the Colon
Wednesday, 3:30–5 p.m.—Surgery of the Spleen
Thursday, 1:30–3 p.m.—Malignant Thyroid Disease

CLINICOPATHOLOGY CONFERENCES

Another innovation this year is the inclusion of two clinicopathology conferences in the program, one on Monday afternoon from 1:30 to 3 p.m. and the second on Wednesday afternoon at the same time.

GYNECOLOGY AND OBSTETRICS

Important panel discussions in this specialty have been planned for three afternoons of the Congress week, as follows:

Wednesday, 1:30–3 p.m.—Physiological Disorders Present in the Toxemias of Pregnancy; 3:30–5 p.m.—Surgical Procedures in the Treatment of Sterility
Thursday, 1:30–3 p.m.—Management and Problems of Prolonged Labor
Friday, 1:30–3 p.m.—Surgical Procedures in Treatment of Special Defects in Pelvic Floor Supports; 3:15–4:45.—Treatment of Cancer of the Cervix

AFTERNOON PANEL DISCUSSIONS, SURGICAL SPECIALTIES

Friday afternoon will be devoted to panel discussion sessions in the surgical specialties. A brief outline of the program follows:

Neurological Surgery
1:30–3 p.m.—The Neurosurgical Treatment of Epilepsy
3:15—4:45 p.m.—Cerebral Vascular Surgery
Orthopedic Surgery
1:30–3 p.m.—Diagnosis and Treatment of Osteogenic Sarcoma
3:15–4:45 p.m.—Benign Bone Lesions Sometimes Mistaken for Sarcoma
Plastic Surgery
1:30–3 p.m.—Management of Compound Facial Injuries
3:15–4:45 p.m.—Reconstructive Surgery of the Hand
Thoracic Surgery
1:30–3 p.m.—Thoracic Emergencies
3:15–4:45 p.m.—Postoperative Problems in Thoracic Surgery
Urology
1:30–3 p.m.—Urological Endocrinology
3:15–4:45 p.m.—Carcinoma of the Prostate; Appraisal of Present Day Treatment

SPECIAL SYMPOSIA

Special symposia have been increased this year, in response to interest in the fields. The Symposium on Trauma will be held on Tuesday afternoon at 2 p.m., the Symposium on Cancer on Wednesday at 2 p.m., a symposium on Graduate Training in Surgery and the Surgical Specialties on Thursday at 1:30, and a Motion Picture Symposium on "Unusual Conditions in Abdominal Surgery" on Thursday evening at 8 p.m.

FORUM ON FUNDAMENTAL SURGICAL PROBLEMS

The unique institution of the Surgical Forum, which annually contributes much to the education

of Congress visitors, will have sessions each day of the Congress week. The Surgical Forum Committee plans 12 Forum sessions this year. Details will be announced as the program develops.

POSTGRADUATE COURSES

Advance interest in the postgraduate courses, running each forenoon Tuesday through Friday from 8:30 to 11:30 a.m., will make it advisable to register for these courses as quickly as possible, since seating space will be limited. The registration fee is $5.00 per course. Courses and chairman are:

Preoperative and Postoperative Care. WALTER G. MADDOCK, Chairman.
Diseases of the Upper Gastrointestinal Tract. JOHN T. REYNOLDS, Chairman.
Surgery of the Small and Large Bowel. R. KENNEDY GILCHRIST, Chairman.
Cardiovascular Surgery. EGBERT H. FELL, Chairman.
Obstetrics and Gynecology. HERBERT E. SCHMITZ, Chairman.
Trauma. JAMES K. STACK, Chairman.

OPHTHALMOLOGY EVENING PANEL DISCUSSIONS

Separate sessions for ophthalmologists will include panel discussions on three evenings. On Tuesday evening at 8:30 the topic will be "Surgery of the Eyelids and Adnexae"; on Wednesday evening at 8:30 the subject will be "Surgical Management of Glaucoma"; and on Thursday evening at the same time the subject will be "Surgical Management of Cataracts."

OTOLARYNGOLOGY EVENING PANEL DISCUSSIONS

Separate sessions for otolaryngologists will also be held on three evenings. "The Tonsil Problem" will be discussed on Tuesday at 8:30 p.m., "Reconstructive Surgery of the Face" on Wednesday evening at 8:30 p.m., and "Menière's Syndrome" on Thursday evening at 8:30 p.m.

MOTION PICTURES AND CINÉ CLINICS

In addition to the splendid program of ciné clinics, three-dimensional films, and television the Committee on Medical Motion Pictures is currently choosing films to be shown. Anyone wishing to contribute medical motion pictures to the Congress film program should forward these pictures for immediate review and approval by the Committee to Dr. H. Prather Saunders, Secretary, Committee on Medical Motion Pictures, 40 East Erie Street, Chicago 11, Illinois.

Ciné clinics are being planned to show, primarily, the ordinary problems of basic surgery. Some specialty and spectacular surgery will be included.

ADVANCE REGISTRATION

To accommodate the large attendance expected, Registration Desk hours at the Conrad Hilton hotel will be increased as follows: Sunday, October 4, from 3 p.m. to 9 p.m.; Monday, October 5, from 8 a.m. to 7:30 p.m.; Tuesday through Friday, 8 a.m. to 5 p.m.

Because advance registration involves only a brief check-in on arrival, a matter of seconds, Fellows planning to attend are urged to follow this more rapid procedure. Scientific sessions will begin promptly on Monday morning, hence it will be advisable to complete the registration process in advance.

No registration fee will be charged Fellows whose dues are paid to December 31, 1952; no registration fee is required of Initiates, Junior Candidates or Surgical Residents. Non-Fellows and Fellows whose dues are not paid will pay a fee of $20.00. It is also suggested that non-Fellows bring medical identification with them, to simplify their registration. Official registration forms have been sent to all Fellows. Others interested in attending may request this material from the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

HOTEL RESERVATIONS

To insure obtaining the accommodations you wish it is desirable that hotel reservations be made in advance. Anyone wishing the official forms or information may request this material from the American College of Surgeons.

SCIENTIFIC AND TECHNICAL EXHIBITS

Forms to be used in applying for scientific exhibit space may be obtained from Dr. Walter E. Batchelder, Chairman, Committee on Scientific Exhibits. Requests may be submitted for consideration through June 30.

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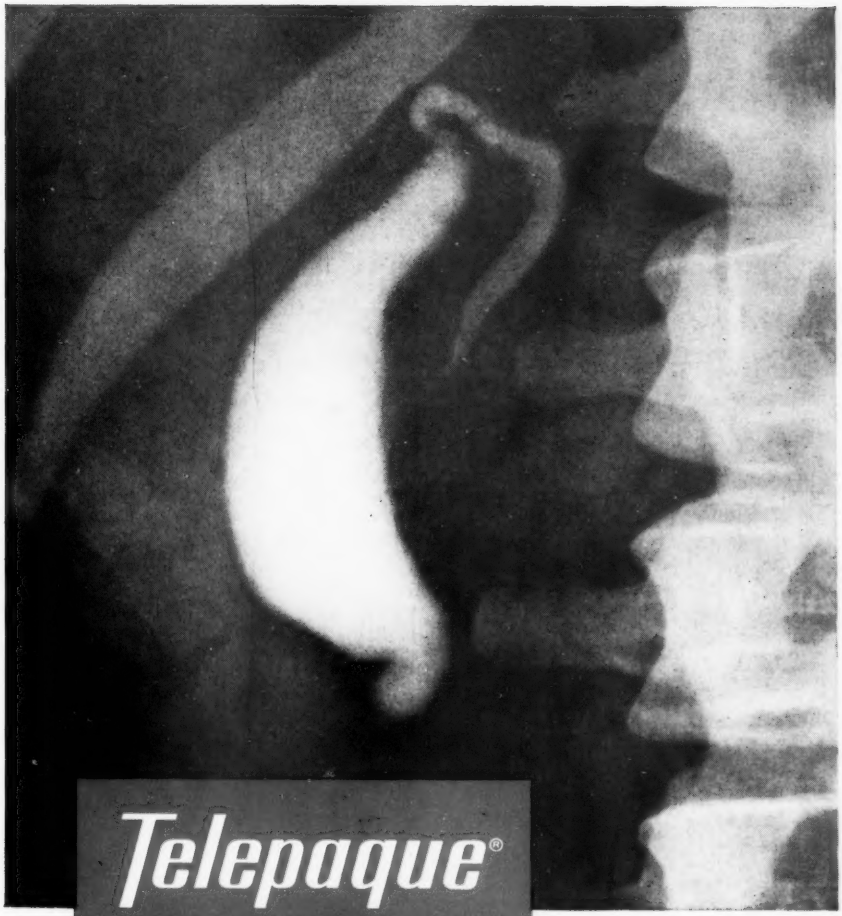

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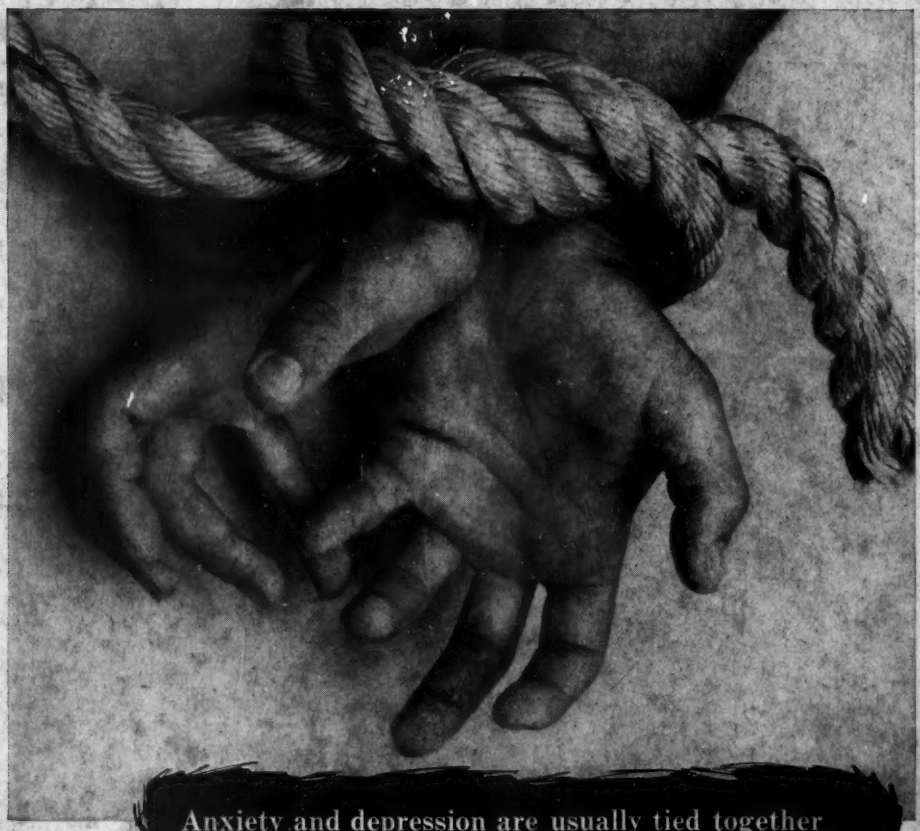

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